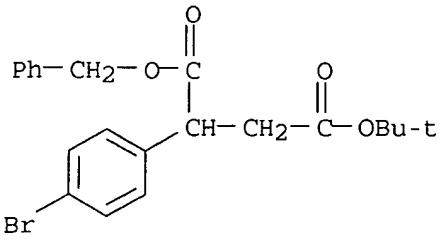
lwk 3/25/07

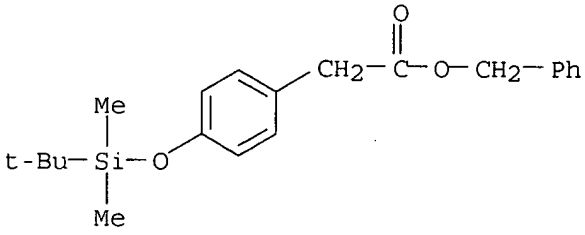
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L1 9 ANSWERS REGISTRY COPYRIGHT 2007 ACS on STN
IN Butanedioic acid, (4-bromophenyl)-, 4-(1,1-dimethylethyl) 1-(phenylmethyl) ester (9CI)
MF C21 H23 Br O4



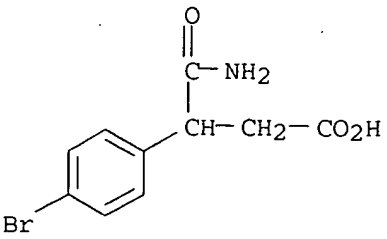
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L1 9 ANSWERS REGISTRY COPYRIGHT 2007 ACS on STN
IN Benzeneacetic acid, 4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-, phenylmethyl ester (9CI)
MF C21 H28 O3 Si



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L1 9 ANSWERS REGISTRY COPYRIGHT 2007 ACS on STN
IN Benzenepropanoic acid, β-(aminocarbonyl)-4-bromo- (9CI)
MF C10 H10 Br N O3



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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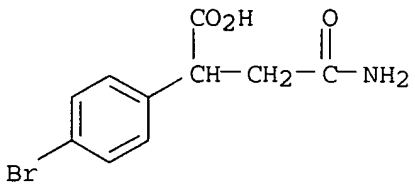
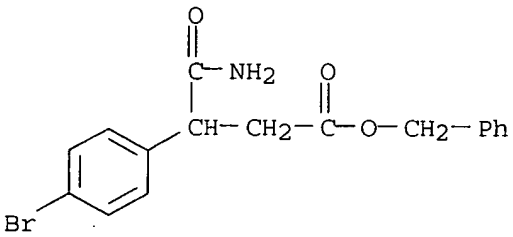
IN Benzeneacetic acid, α-(2-amino-2-oxoethyl)-4-bromo- (9CI)
MF C10 H10 Br N O3



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L1 9 ANSWERS REGISTRY COPYRIGHT 2007 ACS on STN
IN Benzenepropanoic acid, β-(aminocarbonyl)-4-bromo-, phenylmethyl ester (9CI)
MF C17 H16 Br N O3



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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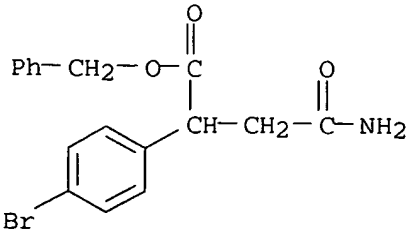
IN Benzeneacetic acid, α-(2-amino-2-oxoethyl)-4-bromo-, phenylmethyl ester (9CI)
MF C17 H16 Br N O3



10/569812MMP Inhibitors REG NO. search

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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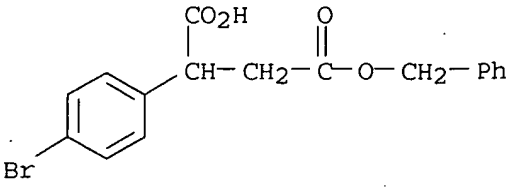
MF C17 H15 Br O4



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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FILE 'REGISTRY' ENTERED AT 18:07:32 ON 25 MAR 2007
L1 9 S 335200-36-7/RN OR 845785-97-9/RN OR 845785-98-0/RN OR 8457

=> fil hcap

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.45	0.66

FILE 'HCAPLUS' ENTERED AT 18:08:19 ON 25 MAR 2007
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FILE COVERS 1907 - 25 Mar 2007 VOL 146 ISS 14
FILE LAST UPDATED: 23 Mar 2007 (20070323/ED)

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This file contains CAS Registry Numbers for easy and accurate

10/569812MMP Inhibitors REG NO. search

substance identification.

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=> s l1
L2            2 L1

=> d l2 1-2 ibib abs

L2   ANSWER 1 OF 2  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2005:158625  HCAPLUS
DOCUMENT NUMBER:          142:261292
TITLE:                    Preparation of (hetero)aryl-substituted succinate
                          derivatives as matrix metalloproteinase inhibitors
INVENTOR(S):              Holmes, Ian; Watson, Stephen Paul
PATENT ASSIGNEE(S):       Glaxo Group Limited, UK
SOURCE:                   PCT Int. Appl., 36 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.          DATE
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            GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
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            NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
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            EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
            SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
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OTHER SOURCE(S):          CASREACT 142:261292; MARPAT 142:261292
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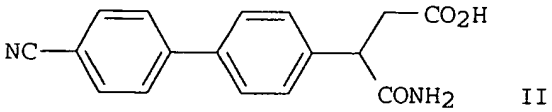

II

AB Title compds. represented by the formula I, R1ZQCH(R2)CH2X, [wherein R1 = (un)substituted alkyl(cycloalkyl), alkylheterocycloalkyl, alkylaryl, etc.; Z = a bond, CH2, O, S, etc.; Q = (un)substituted (hetero)aryl; X = COR3; R2 = CONH2, CO2H, sulfonylamino, etc.; R3 = OH, oxyalkyl or

(un)substituted amino; with a proviso; and physiol. functional derivs. thereof] were prepared as matrix metalloproteinase (MMP) inhibitors. Coupling reaction of 4-amino-3-(4-bromophenyl)-4-oxobutanoic acid with p-nitrilephenylboronic acid gave II in 100% yield. I showed inhibition of MMP-12 with IC50 values of below 100 μM. Thus, I and their pharmaceutical compns. are useful as matrix metalloproteinase inhibitors for the treatment of inflammation or autoimmune disease (no data).

L2 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:8060 HCAPLUS
DOCUMENT NUMBER: 134:307022
TITLE: Antibody-catalyzed hydrolysis of oligomeric esters: a model for the degradation of polymeric materials
AUTHOR(S): Brummer, Oliver; Hoffman, Timothy Z.; Chen, Da-Wei; Janda, Kim D.
CORPORATE SOURCE: Department of Chemistry, The Scripps Research Institute and The Skaggs Institute for Chemical Biology, La Jolla, CA, 92037, USA
SOURCE: Chemical Communications (Cambridge) (2001), (1), 19-20
CODEN: CHCOFS; ISSN: 1359-7345
PUBLISHER: Royal Society of Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 134:307022
AB A catalytic antibody has been discovered that degrades oligomeric ester substrates. All the observations and data confirmed that the antibody performed oligomer degrdns. by 'multimer' processing using nonregioselective, kinetically biased endo-cleavage, rather than a stepwise deoligomerization through cleavage of monomers from a terminus. These findings are of fundamental importance as now catalytic antibodies share another trait thought only to be associated with enzymes, the biodegrdn. of oligo and polymeric materials.
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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FULL ESTIMATED COST                                10.86      11.52

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)      SINCE FILE      TOTAL
                                                   ENTRY    SESSION
CA SUBSCRIBER PRICE                                -1.56      -1.56

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STRUCTURE FILE UPDATES:   23 MAR 2007  HIGHEST RN 928114-47-0
DICTIONARY FILE UPDATES:  23 MAR 2007  HIGHEST RN 928114-47-0

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experimental property data in the original document.  For information
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http://www.cas.org/ONLINE/UG/regprops.html

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10/569812MMP Inhibitors REG NO. search

845786-06-3 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
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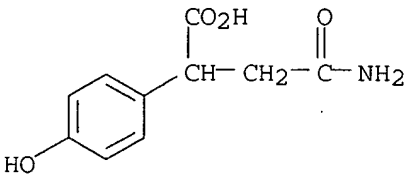
=> d scan

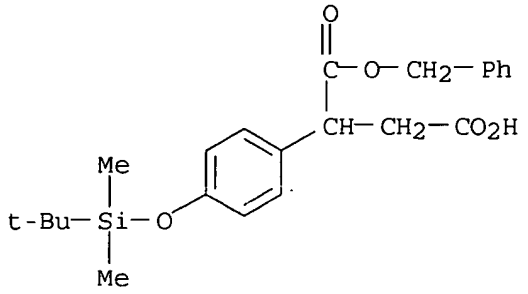
L4 9 ANSWERS REGISTRY COPYRIGHT 2007 ACS on STN
IN Benzeneacetic acid, α-(2-amino-2-oxoethyl)-4-hydroxy- (9CI)
MF C10 H11 N O4



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):9

L4 9 ANSWERS REGISTRY COPYRIGHT 2007 ACS on STN
IN Butanedioic acid, [4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]phenyl]-, 1-(phenylmethyl) ester (9CI)
MF C23 H30 O5 Si



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L4 9 ANSWERS REGISTRY COPYRIGHT 2007 ACS on STN
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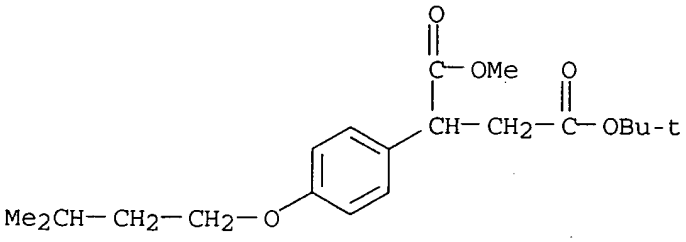
MF C20 H30 O5



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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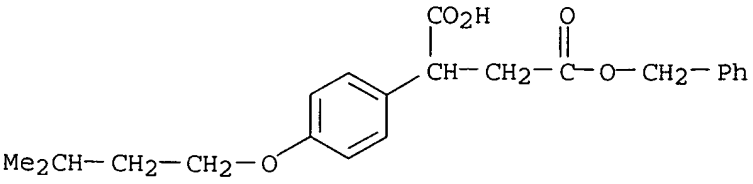
MF C22 H26 O5



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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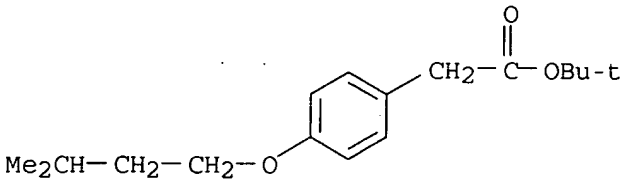
MF C17 H26 O3



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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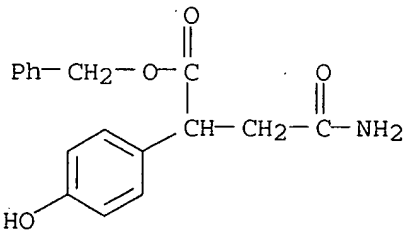

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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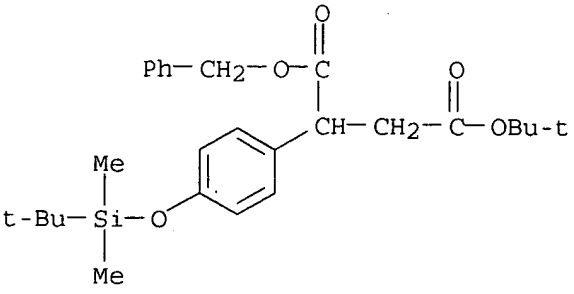
MF C27 H38 O5 Si



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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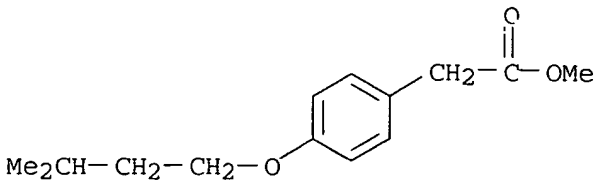

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L4 9 ANSWERS REGISTRY COPYRIGHT 2007 ACS on STN
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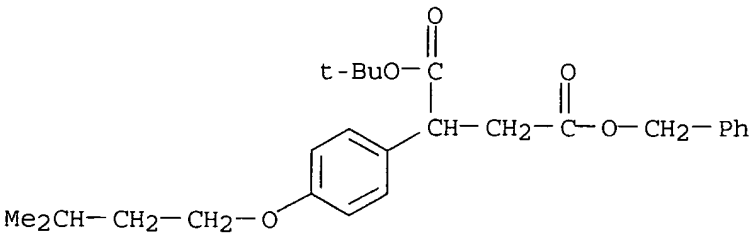

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.45	11.97

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-1.56

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FILE LAST UPDATED: 23 Mar 2007 (20070323/ED)

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=> d his

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FILE 'HCAPLUS' ENTERED AT 18:08:19 ON 25 MAR 2007
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L3 1 S 845786-06-3/RN OR 845786-07-4/RN OR 845786-08-5/RN OR 8457

FILE 'REGISTRY' ENTERED AT 18:09:41 ON 25 MAR 2007
L4 9 S 845786-06-3/RN OR 845786-07-4/RN OR 845786-08-5/RN OR 8457

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L5 1 L4

=> d ibib abs

L5 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:158625 HCAPLUS
DOCUMENT NUMBER: 142:261292
TITLE: Preparation of (hetero)aryl-substituted succinate derivatives as matrix metalloproteinase inhibitors
INVENTOR(S): Holmes, Ian; Watson, Stephen Paul
PATENT ASSIGNEE(S): Glaxo Group Limited, UK
SOURCE: PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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WO 2005016868	A3	20050519		

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R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, HR			
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US 2006235074	A1	20061019	US 2006-569812 20060210
PRIORITY APPLN. INFO.:			GB 2003-19069 A 20030814
			WO 2004-EP9087 W 20040812

OTHER SOURCE(S): CASREACT 142:261292; MARPAT 142:261292
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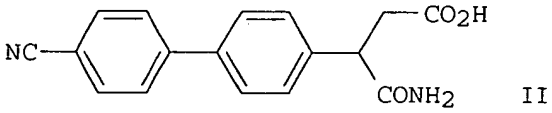

II

AB Title compds. represented by the formula I, R1ZQCH(R2)CH2X, [wherein R1 = (un)substituted alkyl(cycloalkyl), alkylheterocycloalkyl, alkylaryl, etc.; Z = a bond, CH2, O, S, etc.; Q = (un)substituted (hetero)aryl; X = COR3; R2 = CONH2, CO2H, sulfonylamino, etc.; R3 = OH, oxyalkyl or (un)substituted amino; with a proviso; and physiol. functional derivs. thereof] were prepared as matrix metalloproteinase (MMP) inhibitors. Coupling reaction of 4-amino-3-(4-bromophenyl)-4-oxobutanoic acid with p-nitrilephenylboronic acid gave II in 100% yield. I showed inhibition of MMP-12 with IC50 values of below 100 μM. Thus, I and their pharmaceutical compns. are useful as matrix metalloproteinase inhibitors for the treatment of inflammation or autoimmune disease (no data).

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	10.63	22.60

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-0.78	-2.34

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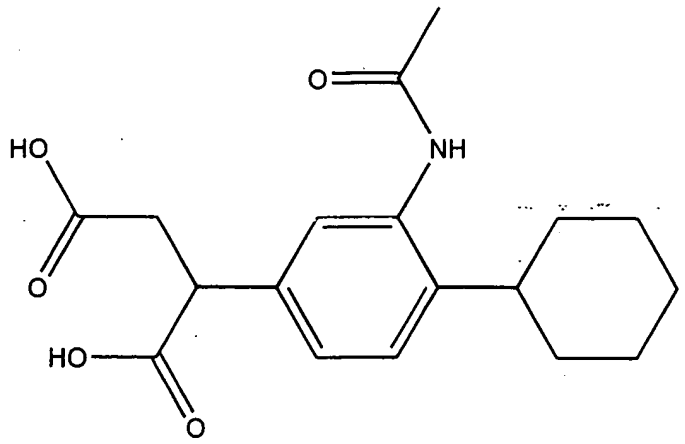
FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Mar 23, 2007 (200

10/569812



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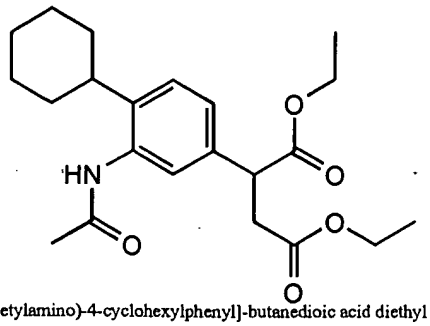

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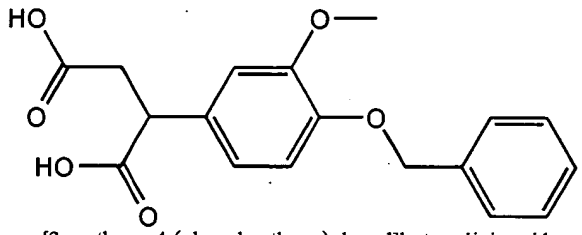

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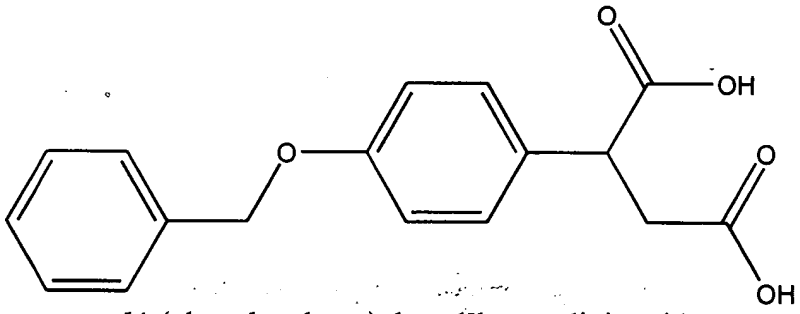

[4-(phenylmethoxy)phenyl]butanedioic acid

biphenylglutaramic acid deriv.

(hetero)aryl-substituted succinate derivatives

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     (FILE 'HOME' ENTERED AT 07:45:47 ON 26 MAR 2007)

     FILE 'REGISTRY' ENTERED AT 07:46:04 ON 26 MAR 2007
L1            0 S "[3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-BUTANEDIOIC ACID"/RN

     FILE 'HCAPLUS' ENTERED AT 07:46:39 ON 26 MAR 2007
                S "[3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-BUTANEDIOIC ACID"/CN

     FILE 'REGISTRY' ENTERED AT 07:46:45 ON 26 MAR 2007
L2            0 S "[3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-BUTANEDIOIC ACID"/CN

     FILE 'HCAPLUS' ENTERED AT 07:46:46 ON 26 MAR 2007
L3            0 S L2
L4            0 S "[3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-BUTANEDIOIC ACID"
L5            0 S "BUTANEDIOIC ACID, [3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-"
L6            1 S "BIPHENYLPENTANOIC ACID"
L7            1 S "(HETERO)ARYL-SUBSTITUTED SUCCINATE"
L8            0 S "[3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-BUTANEDIOIC ACID"
L9            0 S "BUTANEDIOIC ACID, [3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-"
L10           0 S "BUTANEDIOIC ACID [3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-"
L11        4510 S "BUTANEDIOIC ACID"
L12           0 S "[3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-"
L13         994 S "CYCLOHEXYLPHENYL]"
L14           0 S L12 AND L13
L15           0 S "CYCLOHEXYLPHENYL" (N) "BUTANEDIOIC ACID"
L16           0 S "CYCLOHEXYLPHENYLBUTANEDIOIC ACID"
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=> s "[3-(acetylamino)-4-cyclohexylphenyl]-butanedioic acid"/cn
   REGISTRY INITIATED
Substance data SEARCH and crossover from CAS REGISTRY in progress...
Use DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.

L3            0 L2

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             1 "ACETYLAMINOS"
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       4341454 "ACID"
       1566176 "ACIDS"
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L4            0 "[3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-BUTANEDIOIC ACID"
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=> s "butanedioic acid,[3-(acetylamino)-4-cyclohexylphenyl]-"
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          6700 "ACETYLAMINO"
             1 "ACETYLAMINOS"
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                 ("ACETYLAMINO" OR "ACETYLAMINOS")
       5548817 "4"
           992 "CYCLOHEXYLPHENYL"
             2 "CYCLOHEXYLPHENYLS"
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                 ("CYCLOHEXYLPHENYL" OR "CYCLOHEXYLPHENYLS")
L5            0 "BUTANEDIOIC ACID,[3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-"
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=> s "biphenylpentanoic acid"
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       4341454 "ACID"
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                 ("ACID" OR "ACIDS")
L6           1 "BIPHENYLPENTANOIC ACID"
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IC    ICM  C07D209-48
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           A61K031-506; A61P029-00
CC    27-11 (Heterocyclic Compounds (One Hetero Atom))
      Section cross-reference(s): 1, 63
TI    Preparation of biphenylpentanoic acid derivatives as
      matrix metalloproteinase inhibitors
ST    isoindolylethyl pyrimidinylethyl biphenylpentanoic acid
      prepn matrix metalloproteinase inhibitor
IT    Anti-inflammatory agents
      Autoimmune disease
      Drug delivery systems
      Human
      Immunomodulators
      Inflammation
         (preparation of biphenylpentanoic acid derivs. as matrix
         metalloproteinase inhibitors)
IT    9004-06-2, MMP 12
      RL: BSU (Biological study, unclassified); BIOL (Biological study)
         (MMP-12; preparation of biphenylpentanoic acid derivs.
         as matrix metalloproteinase inhibitors)
IT    848407-30-7P, 5-(Biphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-
      yl)ethyl]-3-hydroxypentanoic acid   848407-34-1P, 5-(Biphenyl-4-yl)-3-
      hydroxy-2-[2-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-
      yl)ethyl]pentanoic acid   848407-35-2P, 5-(Biphenyl-4-yl)-3-hydroxy-2-[2-
      (3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)ethyl]pentanoic acid
      848407-36-3P, 5-(4'-Acetylbiphenyl-4-yl)-3-hydroxy-2-[2-(3-methyl-2,4-
      dioxo-3,4-dihydropyrimidin-1(2H)-yl)ethyl]pentanoic acid   848407-38-5P,
      3-Hydroxy-2-[2-(3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)ethyl]-5-
      [4-(pyrimidin-5-yl)phenyl]pentanoic acid   848407-39-6P,
      3-Hydroxy-2-[2-(3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)ethyl]-5-
      [4'-(trifluoromethoxy)biphenyl-4-yl]pentanoic acid   848407-40-9P,
      5-[4-(Benzo[b]furan-2-yl)phenyl]-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-
      yl)ethyl]-3-hydroxypentanoic acid   848407-42-1P, 2-[2-(1,3-Dioxo-1,3-
      dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(trifluoromethoxy)biphenyl-
      4-yl]pentanoic acid   848407-43-2P, 2-[2-(1,3-Dioxo-1,3-dihydro-2H-
      isoindol-2-yl)ethyl]-3-hydroxy-5-[4'-(methylthio)biphenyl-4-yl]pentanoic
      acid   848407-44-3P, 5-(4'-Cyanobiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-
      2H-isoindol-2-yl)ethyl]-3-hydroxypentanoic acid   848407-45-4P,
      5-(4'-Acetylbiphenyl-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-
      yl)ethyl]-3-hydroxypentanoic acid   848407-46-5P, 2-[2-(1,3-Dioxo-1,3-
      dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-[4-(pyrimidin-5-
      yl)phenyl]pentanoic acid
      RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU
      (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
      (Uses)
         (preparation of biphenylpentanoic acid derivs. as matrix
         metalloproteinase inhibitors)
IT    608-34-4, 3-Methyl-2,4(1H,3H)-pyrimidinedione   1074-82-4, Potassium
      phthalimide   1694-31-1, tert-Butyl acetoacetate   3597-91-9,
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Biphenyl-4-ylmethanol 16004-15-2, 4-Iodobenzyl bromide 86864-60-0, (2-Bromoethoxy)tert-butyldimethylsilane 89238-99-3, 2,2,2-Trichloroethanimidic acid 4-Methoxybenzyl ester 98437-24-2, Benzofuran-2-ylboronic acid 149104-90-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of biphenylpentanoic acid derivs. as matrix metalloproteinase inhibitors)

IT 2567-29-5P, 4-Bromomethylbiphenyl 811456-29-8P, 5-(Biphenyl-4-yl)-3-oxopentanoic acid tert-butyl ester 811456-40-3P, 5-(4-Iodophenyl)-3-oxopentanoic acid tert-butyl ester 848407-32-9P, 1,1-Dimethylethyl 5-(biphenyl-4-yl)-3-[[[4-(methyloxy)phenyl]methyl]oxy]-2-[2-[(methylsulfonyl)oxy]ethyl]pentanoate 848407-37-4P, 3-Hydroxy-5-(4-iodophenyl)-2-[2-(3-methyl-2,4-dioxo-3,4-dihydro-1(2H)-pyrimidinyl)ethyl]pentanoic acid 848407-41-0P, 2-[2-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-3-hydroxy-5-(4-iodophenyl)pentanoic acid 848407-47-6P, tert-Butyl 5-(biphenyl-4-yl)-2-[2-[(tert-butyldimethylsilyl)oxy]ethyl]-3-oxopentanoate 848407-48-7P, tert-Butyl 5-(biphenyl-4-yl)-2-[2-[(tert-butyldimethylsilyl)oxy]ethyl]-3-hydroxypentanoate 848407-49-8P 848407-50-1P, 1,1-Dimethylethyl 5-(biphenyl-4-yl)-2-(2-hydroxyethyl)-3-[[[4-(methyloxy)phenyl]methyl]oxy]pentanoate 848407-51-2P 848407-52-3P 848407-53-4P 848407-54-5P, 1,1-Dimethylethyl 2-(2-hydroxyethyl)-5-(4-iodophenyl)-3-[[[4-(methyloxy)phenyl]methyl]oxy]pentanoate 848407-55-6P, 1,1-Dimethylethyl 5-(4-iodophenyl)-3-[[[4-(methyloxy)phenyl]methyl]oxy]-2-[2-[(methylsulfonyl)oxy]ethyl]pentanoate 848407-56-7P, 1,1-Dimethylethyl 2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-5-(4-iodophenyl)-3-[[[4-(methyloxy)phenyl]methyl]oxy]pentanoate 848407-57-8P, 1,1-Dimethylethyl 5-(4-iodophenyl)-2-[2-(3-methyl-2,4-dioxo-3,4-dihydro-1(2H)-pyrimidinyl)ethyl]-3-[[[4-(methyloxy)phenyl]methyl]oxy]pentanoate
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of biphenylpentanoic acid derivs. as matrix metalloproteinase inhibitors)

ALL ANSWERS HAVE BEEN SCANNED

=> d ibib abs

L6 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:	2005:260025 HCAPLUS
DOCUMENT NUMBER:	142:336245
TITLE:	Preparation of biphenylpentanoic acid derivatives as matrix metalloproteinase inhibitors
INVENTOR(S):	Gaines, Simon; Holmes, Ian Peter; Martin, Stephen Lewis; Watson, Stephen Paul
PATENT ASSIGNEE(S):	Glaxo Group Limited, UK
SOURCE:	PCT Int. Appl., 41 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005026120	A1	20050324	WO 2004-EP10319	20040910

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AU 2004272280	A1	20050324	AU 2004-272280		20040910
CA 2538315	A1	20050324	CA 2004-2538315		20040910
EP 1663970	A1	20060607	EP 2004-765231		20040910
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CN 1849306	A	20061018	CN 2004-80026229		20040910
BR 2004013791	A	20061107	BR 2004-13791		20040910
JP 2007505081	T	20070308	JP 2006-525794		20040910
NO 2006000540	A	20060404	NO 2006-540		20060202
US 2006293353	A1	20061228	US 2006-571443		20060313
PRIORITY APPLN. INFO.:			GB 2003-21538	A	20030913
			WO 2004-EP10319	W	20040910

OTHER SOURCE(S): CASREACT 142:336245; MARPAT 142:336245

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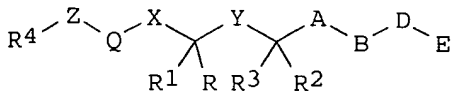

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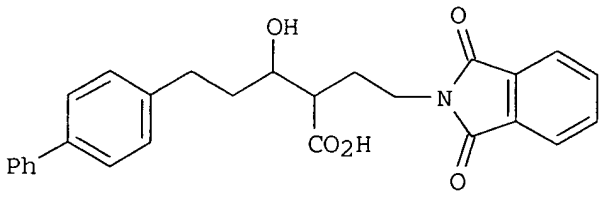

II

AB Title compds. represented by the formula I [wherein A = a bond or (CH:CH)alkyl; B = a bond, O, S, SO2, CO, etc.; D = a bond or alkyl; E = (un)substituted (hetero)aryl; Q = (un)substituted (hetero)aryl; X = O, S, SO, SO2, CO, etc.; Y = SO, SO2, CS, etc.; R, R1 = independently H or alkyl(aryl); R2 = carboxy, amido, thiol, etc.; R3 = H or alkyl(aryl); R4 = (un)substituted (hetero)aryl; Z = a bond, CH2, amino, etc., or R4Z = (un)substituted fused tricyclic group; and physiol. functional derivs. thereof] were prepared as matrix metalloproteinase (MMP) inhibitors. For example, II was given in a multi-step synthesis starting from biphenyl-4-ylmethanol. I showed inhibition of MMP-12 with IC50 values of below 100 μM. Thus, I and their pharmaceutical compns. are useful as MMP inhibitors for the treatment of autoimmune disorder or inflammatory condition (no data).

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> s "(hetero)aryl-substituted succinate"
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             4 "HETEROS"
         30441 "HETERO"
                 ("HETERO" OR "HETEROS")
        216098 "ARYL"
           562 "ARYLS"
        216403 "ARYL"
                 ("ARYL" OR "ARYLS")
        495465 "SUBSTITUTED"
         51093 "SUCCINATE"
          1228 "SUCCINATES"
         51616 "SUCCINATE"
                 ("SUCCINATE" OR "SUCCINATES")
L7           1 "(HETERO)ARYL-SUBSTITUTED SUCCINATE"
                 ("HETERO"(W)"ARYL"(W)"SUBSTITUTED"(W)"SUCCINATE")

=> d ibib abs

L7   ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2005:158625  HCAPLUS
DOCUMENT NUMBER:          142:261292
TITLE:                    Preparation of (hetero)aryl-
                          substituted succinate derivatives as
                          matrix metalloproteinase inhibitors
INVENTOR(S):              Holmes, Ian; Watson, Stephen Paul
PATENT ASSIGNEE(S):       Glaxo Group Limited, UK
SOURCE:                   PCT Int. Appl., 36 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.          DATE
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     WO 2005016868         A2    20050224    WO 2004-EP9087           20040812
     WO 2005016868         A3    20050519
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             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
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         RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
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             EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
             SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
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     EP 1654218            A2    20060510    EP 2004-764084           20040812
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     JP 2007502259         T     20070208    JP 2006-522996           20040812
     US 2006235074         A1    20061019    US 2006-569812           20060210
PRIORITY APPLN. INFO.:                       GB 2003-19069        A   20030814
                                             WO 2004-EP9087       W   20040812
OTHER SOURCE(S):          CASREACT 142:261292; MARPAT 142:261292
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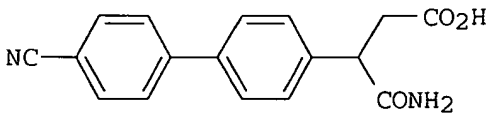

II

AB Title compds. represented by the formula I, R1ZQCH(R2)CH2X, [wherein R1 = (un)substituted alkyl(cycloalkyl), alkylheterocycloalkyl, alkylaryl, etc.; Z = a bond, CH2, O, S, etc.; Q = (un)substituted (hetero)aryl; X = COR3; R2 = CONH2, CO2H, sulfonylamino, etc.; R3 = OH, oxyalkyl or (un)substituted amino; with a proviso; and physiol. functional derivs. thereof] were prepared as matrix metalloproteinase (MMP) inhibitors. Coupling reaction of 4-amino-3-(4-bromophenyl)-4-oxobutanoic acid with p-nitrilephenylboronic acid gave II in 100% yield. I showed inhibition of MMP-12 with IC50 values of below 100 μM. Thus, I and their pharmaceutical compns. are useful as matrix metalloproteinase inhibitors for the treatment of inflammation or autoimmune disease (no data).

```
=> s "[3-(acetylamino)-4-cyclohexylphenyl]-butanedioic acid"
       6851582 "3"
          6700 "ACETYLAMINO"
             1 "ACETYLAMINOS"
          6701 "ACETYLAMINO"
                 ("ACETYLAMINO" OR "ACETYLAMINOS")
       5548817 "4"
           992 "CYCLOHEXYLPHENYL"
             2 "CYCLOHEXYLPHENYLS"
           994 "CYCLOHEXYLPHENYL"
                 ("CYCLOHEXYLPHENYL" OR "CYCLOHEXYLPHENYLS")
          4594 "BUTANEDIOIC"
       4341454 "ACID"
       1566176 "ACIDS"
       4837468 "ACID"
                 ("ACID" OR "ACIDS")
L8           0 "[3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-BUTANEDIOIC ACID"
                 ("3"(W)"ACETYLAMINO"(W)"4"(W)"CYCLOHEXYLPHENYL"(W)"BUTANEDIOIC
                 "(W)"ACID")

=> s "butanedioic acid,[3-(acetylamino)-4-cyclohexylphenyl]-"
          4594 "BUTANEDIOIC"
       4341454 "ACID"
       1566176 "ACIDS"
       4837468 "ACID"
                 ("ACID" OR "ACIDS")
       6851582 "3"
          6700 "ACETYLAMINO"
             1 "ACETYLAMINOS"
          6701 "ACETYLAMINO"
                 ("ACETYLAMINO" OR "ACETYLAMINOS")
       5548817 "4"
           992 "CYCLOHEXYLPHENYL"
             2 "CYCLOHEXYLPHENYLS"
           994 "CYCLOHEXYLPHENYL"
                 ("CYCLOHEXYLPHENYL" OR "CYCLOHEXYLPHENYLS")
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L9            0 "BUTANEDIOIC ACID,[3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-"
                  ("BUTANEDIOIC"(W)"ACID"(W)"3"(W)"ACETYLAMINO"(W)"4"(W)"CYCLOHE
                  XYLPHENYL")

=> s "butanedioic acid [3-(acetylamino)-4-cyclohexylphenyl]-"
          4594 "BUTANEDIOIC"
       4341454 "ACID"
       1566176 "ACIDS"
       4837468 "ACID"
                  ("ACID" OR "ACIDS")
       6851582 "3"
          6700 "ACETYLAMINO"
             1 "ACETYLAMINOS"
          6701 "ACETYLAMINO"
                  ("ACETYLAMINO" OR "ACETYLAMINOS")
       5548817 "4"
           992 "CYCLOHEXYLPHENYL"
             2 "CYCLOHEXYLPHENYLS"
           994 "CYCLOHEXYLPHENYL"
                  ("CYCLOHEXYLPHENYL" OR "CYCLOHEXYLPHENYLS")
L10           0 "BUTANEDIOIC ACID [3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-"
                  ("BUTANEDIOIC"(W)"ACID"(W)"3"(W)"ACETYLAMINO"(W)"4"(W)"CYCLOHE
                  XYLPHENYL")

=> s "butanedioic acid"
          4594 "BUTANEDIOIC"
       4341454 "ACID"
       1566176 "ACIDS"
       4837468 "ACID"
                  ("ACID" OR "ACIDS")
L11       4510 "BUTANEDIOIC ACID"
                  ("BUTANEDIOIC"(W)"ACID")

=> s "[3-(acetylamino)-4-cyclohexylphenyl]-"
       6851582 "3"
          6700 "ACETYLAMINO"
             1 "ACETYLAMINOS"
          6701 "ACETYLAMINO"
                  ("ACETYLAMINO" OR "ACETYLAMINOS")
       5548817 "4"
           992 "CYCLOHEXYLPHENYL"
             2 "CYCLOHEXYLPHENYLS"
           994 "CYCLOHEXYLPHENYL"
                  ("CYCLOHEXYLPHENYL" OR "CYCLOHEXYLPHENYLS")
L12           0 "[3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-"
                  ("3"(W)"ACETYLAMINO"(W)"4"(W)"CYCLOHEXYLPHENYL")

=> s "cyclohexylphenyl]"
           992 "CYCLOHEXYLPHENYL"
             2 "CYCLOHEXYLPHENYLS"
L13        994 "CYCLOHEXYLPHENYL]"
                  ("CYCLOHEXYLPHENYL" OR "CYCLOHEXYLPHENYLS")

=> d his

     (FILE 'HOME' ENTERED AT 07:45:47 ON 26 MAR 2007)

     FILE 'REGISTRY' ENTERED AT 07:46:04 ON 26 MAR 2007
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```
L1             0 S "[3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-BUTANEDIOIC ACID"/RN

     FILE 'HCAPLUS' ENTERED AT 07:46:39 ON 26 MAR 2007
                S "[3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-BUTANEDIOIC ACID"/CN

     FILE 'REGISTRY' ENTERED AT 07:46:45 ON 26 MAR 2007
L2             0 S "[3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-BUTANEDIOIC ACID"/CN

     FILE 'HCAPLUS' ENTERED AT 07:46:46 ON 26 MAR 2007
L3             0 S L2
L4             0 S "[3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-BUTANEDIOIC ACID"
L5             0 S "BUTANEDIOIC ACID, [3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-"
L6             1 S "BIPHENYLPENTANOIC ACID"
L7             1 S "(HETERO)ARYL-SUBSTITUTED SUCCINATE"
L8             0 S "[3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-BUTANEDIOIC ACID"
L9             0 S "BUTANEDIOIC ACID, [3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-"
L10            0 S "BUTANEDIOIC ACID [3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-"
L11         4510 S "BUTANEDIOIC ACID"
L12            0 S "[3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-"
L13          994 S "CYCLOHEXYLPHENYL]"

=> s l12 and l13
L14            0 L12 AND L13

=> s "cyclohexylphenyl" (n) "butanedioic acid"
             992 "CYCLOHEXYLPHENYL"
               2 "CYCLOHEXYLPHENYLS"
             994 "CYCLOHEXYLPHENYL"
                   ("CYCLOHEXYLPHENYL" OR "CYCLOHEXYLPHENYLS")
            4594 "BUTANEDIOIC"
         4341454 "ACID"
         1566176 "ACIDS"
         4837468 "ACID"
                   ("ACID" OR "ACIDS")
            4510 "BUTANEDIOIC ACID"
                   ("BUTANEDIOIC"(W)"ACID")
L15            0 "CYCLOHEXYLPHENYL" (A) "BUTANEDIOIC ACID"

=> s "cyclohexylphenylbutanedioic acid"
               0 "CYCLOHEXYLPHENYLBUTANEDIOIC"
         4341454 "ACID"
         1566176 "ACIDS"
         4837468 "ACID"
                   ("ACID" OR "ACIDS")
L16            0 "CYCLOHEXYLPHENYLBUTANEDIOIC ACID"
                   ("CYCLOHEXYLPHENYLBUTANEDIOIC"(W)"ACID")

=> d his

     (FILE 'HOME' ENTERED AT 07:45:47 ON 26 MAR 2007)

     FILE 'REGISTRY' ENTERED AT 07:46:04 ON 26 MAR 2007
L1             0 S "[3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-BUTANEDIOIC ACID"/RN

     FILE 'HCAPLUS' ENTERED AT 07:46:39 ON 26 MAR 2007
                S "[3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-BUTANEDIOIC ACID"/CN

     FILE 'REGISTRY' ENTERED AT 07:46:45 ON 26 MAR 2007
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L2            0 S "[3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-BUTANEDIOIC ACID"/CN

     FILE 'HCAPLUS' ENTERED AT 07:46:46 ON 26 MAR 2007
L3            0 S L2
L4            0 S "[3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-BUTANEDIOIC ACID"
L5            0 S "BUTANEDIOIC ACID, [3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-"
L6            1 S "BIPHENYLPENTANOIC ACID"
L7            1 S "(HETERO)ARYL-SUBSTITUTED SUCCINATE"
L8            0 S "[3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-BUTANEDIOIC ACID"
L9            0 S "BUTANEDIOIC ACID, [3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-"
L10           0 S "BUTANEDIOIC ACID [3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-"
L11        4510 S "BUTANEDIOIC ACID"
L12           0 S "[3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-"
L13         994 S "CYCLOHEXYLPHENYL]"
L14           0 S L12 AND L13
L15           0 S "CYCLOHEXYLPHENYL" (N) "BUTANEDIOIC ACID"
L16           0 S "CYCLOHEXYLPHENYLBUTANEDIOIC ACID"
```

10/569812MMP Inhibitors Negative Provisos

=> d his

(FILE 'HOME' ENTERED AT 07:45:47 ON 26 MAR 2007)

FILE 'REGISTRY' ENTERED AT 07:46:04 ON 26 MAR 2007
L1 0 S "[3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-BUTANEDIOIC ACID"/RN

FILE 'HCAPLUS' ENTERED AT 07:46:39 ON 26 MAR 2007
S "[3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-BUTANEDIOIC ACID"/CN

FILE 'REGISTRY' ENTERED AT 07:46:45 ON 26 MAR 2007
L2 0 S "[3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-BUTANEDIOIC ACID"/CN

FILE 'HCAPLUS' ENTERED AT 07:46:46 ON 26 MAR 2007
L3 0 S L2
L4 0 S "[3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-BUTANEDIOIC ACID"
L5 0 S "BUTANEDIOIC ACID, [3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-"
L6 1 S "BIPHENYLPENTANOIC ACID"
L7 1 S "(HETERO)ARYL-SUBSTITUTED SUCCINATE"
L8 0 S "[3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-BUTANEDIOIC ACID"
L9 0 S "BUTANEDIOIC ACID, [3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-"
L10 0 S "BUTANEDIOIC ACID [3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-"
L11 4510 S "BUTANEDIOIC ACID"
L12 0 S "[3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-"
L13 994 S "CYCLOHEXYLPHENYL]"
L14 0 S L12 AND L13
L15 0 S "CYCLOHEXYLPHENYL" (N) "BUTANEDIOIC ACID"
L16 0 S "CYCLOHEXYLPHENYLBUTANEDIOIC ACID"
L17 0 S "[3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-BUTANEDIOIC ACID DIETHY
SET POST
L18 0 S "[3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-BUTANEDIOIC ACID DIETHY
L19 0 S "[3-METHOXY-4-(PHENYLMETHOXY)PHENYL] BUTANEDIOIC ACID"

(STIC) INVENTOR SEARCH by S. Sharma Rec'd 3/26/07

Louisa 10569812

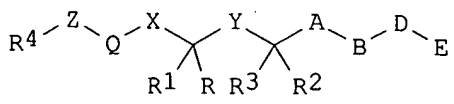
=> d ibib abs hitstr retable l18 1-17;d ibib abs l18 18-44

L18 ANSWER 1 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2005:260025 HCAPLUS
DOCUMENT NUMBER: 142:336245
TITLE: Preparation of biphenylpentanoic acid derivatives as matrix ***metalloproteinase*** inhibitors
INVENTOR(S): Gaines, Simon; ***Holmes, Ian Peter***; Martin, Stephen Lewis; ***Watson, Stephen Paul***
PATENT ASSIGNEE(S): Glaxo Group Limited, UK
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005026120	A1	20050324	WO 2004-EP10319	20040910
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004272280	A1	20050324	AU 2004-272280	20040910
CA 2538315	A1	20050324	CA 2004-2538315	20040910
EP 1663970	A1	20060607	EP 2004-765231	20040910
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, HR				
CN 1849306	A	20061018	CN 2004-80026229	20040910
BR 2004013791	A	20061107	BR 2004-13791	20040910
JP 2007505081	T	20070308	JP 2006-525794	20040910
NO 2006000540	A	20060404	NO 2006-540	20060202
US 2006293353	A1	20061228	US 2006-571443	20060313

PRIORITY APPLN. INFO.: GB 2003-21538 A 20030913
WO 2004-EP10319 W 20040910

OTHER SOURCE(S): CASREACT 142:336245; MARPAT 142:336245
GI



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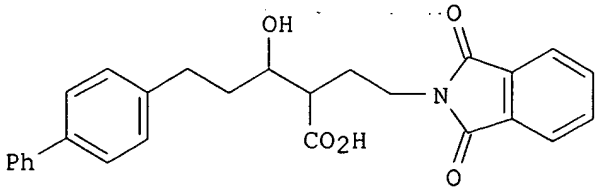


II

AB Title compds. represented by the formula I [wherein A = a bond or (CH:CH)alkyl; B = a bond, O, S, SO2, CO, etc.; D = a bond or alkyl; E = (un)substituted (hetero)aryl; Q = (un)substituted (hetero)aryl; X = O, S, SO, SO2, CO, etc.; Y = SO, SO2, CS, etc.; R, R1 = independently H or alkyl(aryl); R2 = carboxy, amido, thiol, etc.; R3 = H or alkyl(aryl); R4 = (un)substituted (hetero)aryl; Z = a bond, CH2, amino, etc., or R4Z = (un)substituted fused tricyclic group; and physiol. functional derivs. thereof] were prepared as matrix ***metalloproteinase*** (MMP) inhibitors. For example, II was given in a multi-step synthesis starting from biphenyl-4-ylmethanol. I showed inhibition of MMP-12 with IC50 values of below 100 μM. Thus, I and their pharmaceutical compns. are useful as MMP inhibitors for the treatment of autoimmune disorder or inflammatory condition (no data).

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Boehringer Ingelheim Ph	2002			WO 02083642 A	HCAPLUS
Brittelli, D	1997			WO 9743238 A	HCAPLUS
Hashizume, H	1994	42	2097	CHEM PHARM BULL	HCAPLUS
Morales, R	2004	341	1063	JOURNAL OF MOLECULAR	HCAPLUS
Natchus, M	2001	44	1060	JOURNAL OF MEDICINAL	HCAPLUS
Squibb Bristol Myers Co	2004			WO 2004012663 A	HCAPLUS

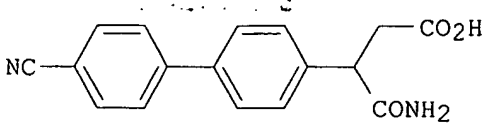
L18 ANSWER 2 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 2

ACCESSION NUMBER: 2005:158625 HCAPLUS
DOCUMENT NUMBER: 142:261292
TITLE: Preparation of (hetero)aryl-substituted succinate derivatives as matrix ***metalloproteinase*** inhibitors
INVENTOR(S): ***Holmes, Ian; Watson, Stephen Paul***
PATENT ASSIGNEE(S): Glaxo Group Limited, UK
SOURCE: PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005016868	A2	20050224	WO 2004-EP9087	20040812
WO 2005016868	A3	20050519		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1654218	A2	20060510	EP 2004-764084	20040812
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, HR				
JP 2007502259	T	20070208	JP 2006-522996	20040812

Louisa 10569812

US 2006235074 A1 20061019 US 2006-569812 20060210
PRIORITY APPLN. INFO.: GB 2003-19069 A 20030814
WO 2004-EP9087 W 20040812
OTHER SOURCE(S): CASREACT 142:261292; MARPAT 142:261292
GI



II

AB Title compds. represented by the formula I, R1ZQCH(R2)CH2X, [wherein R1 = (un)substituted alkyl(cycloalkyl), alkylheterocycloalkyl, alkylaryl, etc.; Z = a bond, CH2, O, S, etc.; Q = (un)substituted (hetero)aryl; X = COR3; R2 = CONH2, CO2H, sulfonylamino, etc.; R3 = OH, oxyalkyl or (un)substituted amino; with a proviso; and physiol. functional derivs. thereof] were prepared as matrix ***metalloproteinase*** (MMP) inhibitors. Coupling reaction of 4-amino-3-(4-bromophenyl)-4-oxobutanoic acid with p-nitrilephenylboronic acid gave II in 100% yield. I showed inhibition of MMP-12 with IC50 values of below 100 μM. Thus, I and their pharmaceutical compns. are useful as matrix ***metalloproteinase*** inhibitors for the treatment of inflammation or autoimmune disease (no data).

L18 ANSWER 3 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2004:1154657 HCAPLUS
DOCUMENT NUMBER: 142:56659
TITLE: Preparation of N-arylglycine derivatives and related compounds as inhibitors of matrix ***metalloproteinase***
INVENTOR(S): ***Holmes, Ian; Watson, Stephen Paul***
PATENT ASSIGNEE(S): Glaxo Group Limited, UK
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004113279	A1	20041229	WO 2004-EP6553	20040616
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1636174	A1	20060322	EP 2004-740011	20040616
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, HR				

JP 2007506664	T	20070322	JP 2006-515980	20040616
US 2006142385	A1	20060629	US 2005-561055	20051216
PRIORITY APPLN. INFO.:			GB 2003-14488 A	20030620
			WO 2004-EP6553 W	20040616

OTHER SOURCE(S): MARPAT 142:56659

AB The invention relates to compds. R1-Z-Q-NR2CH2-X [R1 is optionally substituted alkyl, alkylaryl, aryl or heteroaryl; Z is a bond, CH2, O, S, SO, SO2, NR4, OCR4R5, CR4R5O, or Z, R1 and Q together form an optionally substituted fused tricyclic group; Q is an optionally substituted 5- or 6-membered aryl or heteroaryl ring; X is COR3 or N(OR8)COR9; R2 is SO2R10 or SO2NR10R11; R3 is OR6, NR6R7 or NR6OH; R4, R5 are independently H, alkyl or alkylaryl; R6, R7 are independently H, alkyl or heteroarylalkyl or NR6R7 is a 5- or 6- membered ring which may have one or more addnl. heteroatoms selected from O, S and N; R8-R11 are independently H or alkyl] and physiol. functional derivs., with the exception of N-(ethoxycarbonyl)-N-[4-(1H-tetrazol-1-yl)phenyl]glycine, for use as inhibitors of matrix ***metalloproteinase*** enzymes (MMPs). Thus, p-NCC6H4C6H4-p-N(SO2Me)CH2CO2H was prepared by alkylation of 4-bromoaniline with tert-Bu bromoacetate, followed by methylsulfonylation, ester cleavage (silica gel in toluene at reflux), and reaction with cyanophenylboronic acid.

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Anon	2002			Interchim Intermedia	
Boehringer Ingelheim Ph	2002			WO 02083642 A1	HCAPLUS
Kotobuki Seiyaku Co Ltd	1999			JP 11236369 A	HCAPLUS
Kuragano, T	2002			WO 0238550 A1	HCAPLUS
Rizzi, J	1996			WO 9627583 A	HCAPLUS

L18 ANSWER 4 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 4

ACCESSION NUMBER:	2004:1127310 HCAPLUS
DOCUMENT NUMBER:	142:74355
TITLE:	Preparation of 5-aryl-3-hydroxypentanoates as matrix ***metalloproteinase*** inhibitors
INVENTOR(S):	Gaines, Simon; ***Holmes, Ian Peter; Watson, Stephen Paul***
PATENT ASSIGNEE(S):	Glaxo Group Limited, UK
SOURCE:	PCT Int. Appl., 37 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004110974	A1	20041223	WO 2004-EP5966	20040601

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,

SN, TD, TG

EP 1654213	A1	20060510	EP 2004-739544		20040601
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, HR					
JP 2006526590	T	20061124	JP 2006-508257		20040601
US 2006160875	A1	20060720	US 2005-559600		20051202
PRIORITY APPLN. INFO.:			GB 2003-12654	A.	20030603
			WO 2004-EP5966	W	20040601

OTHER SOURCE(S): MARPAT 142:74355

AB R4ZQXCR1R1'YCR2R3R3' [I; Q = (substituted) 5-6-membered aryl, heteroaryl; X = O, S, NR5, CR6R7; Y = CHOH, CHSH, NOR8, CNR8, CNOR8; Z = bond, CR10R11, O,S,SO,SO2, NR10, OCR10R11, CR10R11O; ZR4Q = atoms to form a (substituted) fused tricyclic group; R1, R1', R3, R3' = H, alkyl, alkylaryl; R2 = CO2R8, CONR5OR9, NR5COR9; R4 = (substituted) 5-6 membered aryl, heteroaryl; R5 = H, alkyl; R6, R7 = H, alkyl, halo; R8, R9 = H, alkyl; R10, R11 = H, alkyl, alkylaryl], were prepared Thus, 5-biphen-4-yl-3-hydroxypentanoic acid (preparation given), diisopropylamine, and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate were stirred together for 5 min. in DMF; thiazolidine was added followed by stirring for 2 h to give 47% 5-biphen-4-yl-3-hydroxy-1-thiazolidin-3-ylpentan-1-one. The latter and addnl. I inhibited MMP-12 with IC50 <100 μM.

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Barron	1968	11	1139	JOURNAL OF MEDICINAL	HCAPLUS
Forsey, P	1998			WO 9809940 A	HCAPLUS
Michael, O	2002			US 6350885 B1	HCAPLUS
Robertson, L	1984	34	1020	EXPERIENTIA	HCAPLUS

L18 ANSWER 5 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 5

ACCESSION NUMBER: 2000:94249 HCAPLUS

DOCUMENT NUMBER: 132:277044

TITLE: Distinct Contributions of Glycoprotein VI and α2β1 Integrin to the Induction of Platelet Protein Tyrosine Phosphorylation and Aggregation

AUTHOR(S): Kamiguti, Aura S.; Theakston, Robert D. G.; ***Watson, Steve P.***; Bon, Cassian; Laing, Gavin D.; Zuzel, Mirko

CORPORATE SOURCE: Department of Haematology, Royal Liverpool Hospital, University of Liverpool, Liverpool, UK

SOURCE: Archives of Biochemistry and Biophysics (2000), 374(2), 356-362
CODEN: ABBIA4; ISSN: 0003-9861

PUBLISHER: Academic Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Platelet activation by collagen depends principally on two receptors, α2β1 integrin (GPIa-IIa) and GPVI. During this activation, the nonreceptor protein tyrosine kinase pp72syk is rapidly phosphorylated, but the precise contribution of α2β1 integrin and GPVI to signaling for this phosphorylation is not clear. We have recently found that proteolysis of platelet α2β1 integrin by the snake venom ***metalloproteinase***, jararhagin, results in inhibition of collagen-induced platelet aggregation and pp72syk phosphorylation. In order to verify whether the treatment of platelets with jararhagin had any effect on GPVI signaling, in this study we stimulated platelets treated with either jararhagin or anti-α2β1 antibody with two GPVI

agonists, an antibody to GPVI and convulxin. Platelet shape change and phosphorylation of pp72syk by both GPVI agonists was preserved, as was the structure and function of GPVI shown by 125I-labeled convulxin binding to immunopptd. GPVI from jararhagin-treated platelets. In contrast, defective platelet aggregation in response to GPVI agonists occurred in both jararhagin-treated and α2β1-blocked platelets. This apparent cosignaling role of α2β1 integrin for platelet aggregation suggests the possibility of a topog. association of this integrin with GPVI. We found that both platelet α2β1 integrin and GPVI coimmunopptd. with αIIbβ3 integrin. Since platelet aggregation requires activation of αIIbβ3 integrin, defective aggregation in the absence of α2β1 suggests that this receptor may provide a signaling link between GPVI and αIIbβ3. Our study therefore demonstrates that platelet signaling leading to pp72syk phosphorylation initiated with GPVI engagement by either convulxin or GPVI antibody does not depend on α2β1 integrin. However, αIIbβ3 integrin may, in this model, require functional α2β1 integrin for its activation. (c) 2000 Academic Press.

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Arai, M	1995	89	124	Br J Haematol	MEDLINE
Asazuma, N	1996	75	648	Thromb Haemostasis	HCAPLUS
Berditchevski, F	1995	270	17784	J Biol Chem	HCAPLUS
Clark, E	1994	269	28859	J Biol Chem	HCAPLUS
Clemetson, J	1999	274	29019	J Biol Chem	HCAPLUS
De Luca, M	1995	206	570	Biochem Biophys Res	HCAPLUS
Francischetti, I	1998	353	239	Arch Biochem Biophys	HCAPLUS
Fujii, C	1994	226	243	Eur J Biochem	HCAPLUS
Gao, J	1997	16	6414	Embo J	HCAPLUS
Gibbins, J	1996	271	18095	J Biol Chem	HCAPLUS
Handa, M	1995	73	521	Thromb Haemostasis	HCAPLUS
Ichinobe, T	1995	270	28029	J Biol Chem	
Inoue, T	1997	272	63	J Biol Chem	
Jandrot-Perrus, M	1997	272	27035	J Biol Chem	HCAPLUS
Kamiguti, A	1996	320	635	Biochem J	HCAPLUS
Kamiguti, A	1997	1335	209	Biochim Biophys Acta	
Kamiguti, A	1998	31	853	Braz J Biol Med Res	HCAPLUS
Kamiguti, A	1997	272	32599	J Biol Chem	HCAPLUS
Keely, P	1996	271	26668	J Biol Chem	HCAPLUS
Kehrel, B	1988	71	1074	Blood	HCAPLUS
Kunicki, T	1988	263	4516	J Biol Chem	HCAPLUS
Laemmli, U	1970	227	680	Nature	HCAPLUS
Moroi, M	1989	84	1440	J Clin Invest	MEDLINE
Nieuwenhuis, H	1985	318	470	Nature	HCAPLUS
Paine, M	1992	267	22869	J Biol Chem	HCAPLUS
Petty, H	1996	17	209	Immunol Today	HCAPLUS
Polgar, J	1997	272	13576	J Biol Chem	HCAPLUS
Prado-Franceschi, J	1981	19	875	Toxicon	HCAPLUS
Rubinstein, E	1994	24	3005	Eur J Immunol	HCAPLUS
Saelman, E	1994	83	1244	Blood	HCAPLUS
Santoro, S	1986	46	913	Cell	HCAPLUS
Santoro, S	1995	74	813	Thromb Haemostasis	HCAPLUS
Savage, B	1998	94	657	Cell	HCAPLUS
Slupsky, J	1997	244	168	Eur J Biochem	HCAPLUS
Sugiyama, T	1987	69	1712	Blood	HCAPLUS
Takada, Y	1989	111	709	J Cell Biol	
Timmons, S	1989	169	11	Methods Enzymol	HCAPLUS

Tsuji, M	1997	272	23528	J Biol Chem	HCAPLUS
Vargaftig, B	1983	92	57	Eur J Pharmacol	HCAPLUS

L18 ANSWER 6 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:458564 HCAPLUS
DOCUMENT NUMBER: 145:139950
TITLE: Isolation and characterization of cotiaractivase, a novel low molecular weight prothrombin activator from the venom of Bothrops cotiara
AUTHOR(S): Senis, Yotis A.; Kim, Paul Y.; Fuller, Gemma L. J.; Garcia, Angel; Prabhakar, Sripadi; Wilkinson, Mark C.; Brittan, Helen; Zitzmann, Nicole; Wait, Robin; Warrell, David A.; ***Watson, Steve P.***; Kamiguti, Aura S.; Theakston, R. David G.; Nesheim, Michael E.; Laing, Gavin D.
CORPORATE SOURCE: Centre for Cardiovascular Sciences, Institute of Biomedical Research, University of Birmingham, Edgbaston, rmingham, B15 2TT, UK
SOURCE: Biochimica et Biophysica Acta, Proteins and Proteomics (2006), 1764(5), 863-871
CODEN: BBAPBW; ISSN: 1570-9639
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In this study, we isolated a novel prothrombin activator from the venom of Bothrops cotiara, a Brazilian lance-headed pit viper (Cotiara, Jararaca preta, Biocotiara), which we have designated "cotiaractivase" (prefix: cotiar- from B. cotiara; suffix: -activase, from prothrombin activating activity). Cotiaractivase was purified using a phenyl-Superose hydrophobic interaction column followed by a Mono-Q anion exchange column. It is a single-chain polypeptide with a mol. weight of 22,931 Da as measured by mass spectroscopy. Cotiaractivase generated active α-thrombin from purified human prothrombin in a Ca2+-dependent manner as assessed by S2238 chromogenic substrate assay and SDS-PAGE. Cotiaractivase cleaved prothrombin at positions Arg271-Thr272 and Arg320-Ile321, which are also cleaved by factor Xa. However, the rate of thrombin generation by cotiaractivase was approx. 60-fold less than factor Xa alone and 17 + 106-fold less than the prothrombinase complex. The enzymic activity of cotiaractivase was inhibited by the chelating agent EDTA, whereas the serine protease inhibitor PMSF had no effect on its activity, suggesting that it is a ***metalloproteinase***. Interestingly, S2238 inhibited cotiaractivase activity non-competitively, suggesting that this toxin contains an exosite that allows it to bind prothrombin independently of its active site. Tandem mass spectrometry and N-terminal sequencing of purified cotiaractivase identified peptides that were identical to regions of the cysteine-rich and disintegrin-like domains of known snake venom ***metalloproteinases***. Cotiaractivase is a unique low mol. weight snake venom prothrombin activator that likely belongs to the ***metalloproteinase*** family of proteins.

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Andrews, R	2001	31	155	Haemostasis	HCAPLUS
Bajzar, L	1990	265	16948	J Biol Chem	HCAPLUS
Brufatto, N	2003	278	6755	J Biol Chem	HCAPLUS
Castro, H	1999	37	1403	Toxicon	HCAPLUS
Fox, J	2005	45	969	Toxicon	HCAPLUS
Francischetti, I	1998	119	21	Comp Biochem Physiol	MEDLINE

Garcia, A	2004	103	2088	Blood	HCAPLUS
Gutierrez, J	2000	82	841	Biochimie	HCAPLUS
Jenny, N	2001		171	Hemostasis and throm	
Kalafatis, M	2005	12	141	Curr Opin Hematol	HCAPLUS
Krishnaswamy, S	1997	36	12080	Biochemistry	HCAPLUS
Lewis, R	2004	24	175	Semin Neurol	
Licklider, L	2002	74	3076	Anal Chem	HCAPLUS
Lu, Q	2005	3	1791	J Thromb Haemost	HCAPLUS
Mann, K	2003	1	1504	J Thromb Haemost	HCAPLUS
Mann, K	1981	80	286	Methods Enzymol	
Nahas, L	1979	41	314	Thromb Haemost	HCAPLUS
Nishida, S	1995	34	1771	Biochemistry	HCAPLUS
Paine, M	1992	267	22869	J Biol Chem	HCAPLUS
Senis, Y	2005	16	191	Platelets	HCAPLUS
Silva, M	2003	369	129	Biochem J	HCAPLUS
Teixeira de, F	2005	100	181	Mem Inst Oswaldo Cru	
Walsh, P	2004	30	461	Semin Thromb Hemost	HCAPLUS
Wijeyewickrema, L	2005	45	1051	Toxicon	HCAPLUS
Zhou, Q	1995	307	411	Biochem J	

L18 ANSWER 7 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:734851 HCAPLUS
DOCUMENT NUMBER: 141:203977
TITLE: Matrix ***metalloproteinase*** expression and activity in human airway smooth muscle cells
AUTHOR(S): Elshaw, Shona R.; Henderson, Neil; Knox, Alan J.; ***Watson, Susan A.***; Buttle, David J.; Johnson, Simon R.
CORPORATE SOURCE: Division of Therapeutics and Molecular Medicine, University Hospital, Queens Medical Centre, University of Nottingham, Nottingham, NG7 2UH, UK
SOURCE: British Journal of Pharmacology (***2004***), 142(8), 1318-1324
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Airway remodeling is a feature of chronic asthma comprising smooth muscle hypertrophy and deposition of extracellular matrix (ECM) proteins. Matrix ***metalloproteinases*** (MMPs) breakdown ECM, are involved in tissue remodeling and have been implicated in airway remodeling. Although mesenchymal cells are an important source of MMPs, little data are available on airway smooth muscle (ASM) derived MMPs. We therefore investigated MMP and tissue ***inhibitor*** of ***metalloproteinase*** (TIMP) production and activity in human ASM cells. MMPs and TIMPs were examined using quant. real-time RT-PCR, Western blotting, zymog. and a quench fluorescence (QF) assay of total MMP activity. The most abundant MMPs were pro-MMP-2, pro- MMP-3, active MMP-3 and MT1-MMP. TIMP-1 and TIMP-2 expression was low in cell lysates but high in conditioned medium. High TIMP secretion was confirmed by the ability of ASM-conditioned medium to ***inhibit*** recombinant MMP-2 in a QF assay. Thrombin increased MMP activity by activation of pro-MMP-2 independent of the conventional smooth muscle thrombin receptors PAR 1 and 4. In conclusion, ASM cells express pro-MMP-2, pro and active MMP-3, MMP-9 and MT1-MMP. Unstimulated cells secrete excess TIMP 1 and 2, preventing proteolytic activity. MMP-2 can be activated by thrombin which may contribute to airway remodeling.
RETABLE

Referenced Author	Year	VOL	PG	Referenced Work	Referenced

(RAU)	(RPY)	(RVL)	(RPG)	(RWK)	File
Andrade-Gordon, P	1999	96	12257	Proc Natl Acad Sci U	HCAPLUS
Butler, G	1998	273	871	J Biol Chem	HCAPLUS
Chambers, L	2003	285	L619	Am J Physiol	HCAPLUS
Dahlen, B	1999	54	590	Thorax	MEDLINE
Dunsmore, S	1998	102	1321	J Clin Invest	HCAPLUS
Foda, H	1999	277	L174	Am J Physiol	HCAPLUS
Freyer, A	2001	25	569	Am J Respir Cell Mol	HCAPLUS
Gabazza, E	1999	177	253	Lung	HCAPLUS
Hauck, R	1999	277	L22	Am J Physiol	HCAPLUS
Hirst, S	2000	23	335	Am J Respir Cell Mol	HCAPLUS
Hirst, S	1996	9	808	Eur Resp J	HCAPLUS
Hollenberg, M	1999	20	271	Trends Pharm Sci	HCAPLUS
Imai, K	1997	322	809	Biochem J	HCAPLUS
Jeffery, P	2000	94	S9	Respir Med	
Johnson, P	2000	162	2145	Am J Respir Crit Car	MEDLINE
Johnson, S	1999	277	L1109	Am J Physiol	HCAPLUS
Johnson, S	1997	18	288	Trends Pharmacol Sci	HCAPLUS
Knight, C	1992	296	263	FEBS Lett	HCAPLUS
Knight, D	2001	108	797	J All Clin Immunol	HCAPLUS
Lafleur, M	2001	357	107	Biochem J	HCAPLUS
Lemjabbar, H	1999	20	903	Am J Respir Cell Mol	HCAPLUS
MacFarlane, S	2001	53	245	Pharmacol Rev	HCAPLUS
Mautino, G	1999	160	324	Am J Respir Crit Car	MEDLINE
Nagase, H	1999	274	21491	J Biol Chem	HCAPLUS
Nystedt, S	1994	91	9208	Proc Natl Acad Sci U	HCAPLUS
Panettieri, J	1995	13	205	Am J Respir Cell Mol	
Pang, L	1998	161	2509	J Immunol	HCAPLUS
Rawlings, N	1990	6	118	Comput Appl Biosci	HCAPLUS
Sower, L	1999	247	422	Exp Cell Res	HCAPLUS
Terada, M	2004	169	373	Am J Respir Crit Car	
Tran, T	2003	138	865	Br J Pharmacol	HCAPLUS
Whitelock, J	1996	271	10079	J Biol Chem	HCAPLUS

L18 ANSWER 8 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:303578 HCAPLUS
DOCUMENT NUMBER: 139:20519
TITLE: Expression and regulation of tissue ***inhibitor*** of ***metalloproteinase***-1 and matrix ***metalloproteinases*** by intestinal myofibroblasts in inflammatory bowel disease
AUTHOR(S): McKaig, Brian C.; McWilliams, Daniel; ***Watson, Sue A.***; Mahida, Yashwant R.
CORPORATE SOURCE: Division of Gastroenterology, University Hospital, Queen's Medical Centre, Nottingham, UK
SOURCE: American Journal of Pathology (***2003***), 162(4), 1355-1360
CODEN: AJPAA4; ISSN: 0002-9440
PUBLISHER: American Society for Investigative Pathology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Intestinal fibrosis and strictures frequently occur in Crohn's disease but not ulcerative colitis. We have recently shown that, compared to myofibroblasts obtained from normal and ulcerative colitis tissue, myofibroblasts isolated from fibrotic Crohn's disease mucosal samples express significantly lower amts. of transforming growth factor (TGF)-β3, but the expression of TGF-β2 was significantly greater. We now report that in myofibroblast cultures established from

fibrotic Crohn's disease mucosal samples there is significantly higher constitutive expression of tissue ***inhibitor*** of ***metalloproteinase*** (TIMP)-1 compared to similar cells isolated from normal or ulcerative colitis tissue. Myofibroblasts derived from normal mucosa and from mucosa affected by ulcerative colitis or Crohn's disease also expressed matrix ***metalloproteinase*** (MMP)-1, MMP-2, and MMP-3 but did not express MMP-9. Recombinant (r) TGF-β1 and rTGF-β2, but not rTGF-β3, induced expression of TIMP-1 in normal intestinal myofibroblasts. These studies illustrate a potential mechanism by which differential expression of isoforms of TGF-β may lead to excessive deposition of extracellular matrix and stricture formation via TIMP-1-mediated ***inhibition*** of MMP activity.

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Bailey, C	1994	47	113	J Clin Pathol	MEDLINE
Baugh, M	1999	117	814	Gastroenterology	HCAPLUS
Border, W	1994	331	1286	N Engl J Med	HCAPLUS
Brew, K	2000	1477	267	Biochim Biophys Acta	HCAPLUS
Gomez, D	1997	74	111	Eur J Cell Biol	HCAPLUS
Graham, M	1995	1	220	Inflamm Bowel Dis	
Graham, M	1995	1	220	Inflamm Bowel Dis	
Heuschkel, R	2000	47	57	Gut	HCAPLUS
Ichiki, Y	1995	104	124	J Invest Dermatol	HCAPLUS
Mahida, Y	1997	273	G1341	Am J Physiol	HCAPLUS
McAlindon, M	1998	115	841	Gastroenterology	MEDLINE
McKaig, B	1999	276	G1087	Am J Physiol	HCAPLUS
McKaig, B	2002	282	C172	Am J Physiol	HCAPLUS
Moore, R	1989	257	G274	Am J Physiol	MEDLINE
Nagase, H	1999	274	21491	J Biol Chem	HCAPLUS
Overall, C	1991	266	14064	J Biol Chem	HCAPLUS
Pender, S	1997	158	1582	J Immunol	HCAPLUS
Plateroti, M	1998	274	G945	Am J Physiol	HCAPLUS
Powell, D	1999	277	C1	Am J Physiol	HCAPLUS
Powell, D	1999	277	C183	Am J Physiol	HCAPLUS
Salmela, M	2002	51	540	Gut	HCAPLUS
Shah, M	1994	107	1137	J Cell Sci	HCAPLUS
Shah, M	1995	108	985	J Cell Sci	HCAPLUS
Vaalamo, M	1998	152	1005	Am J Pathol	HCAPLUS
van Tol, E	1999	277	G245	Am J Physiol	HCAPLUS
Von Lampe, B	2000	47	63	Gut	HCAPLUS

L18 ANSWER 9 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:152302 HCAPLUS
DOCUMENT NUMBER: 137:275075
TITLE: Effect of preoperative radiotherapy on matrilysin gene expression in rectal cancer
AUTHOR(S): Kumar, A.; Collins, H.; Van Tam, J.; Scholefield, J. H.; ***Watson, S. A.***
CORPORATE SOURCE: Section of Surgery, University Hospital, Academic Unit of Cancer Studies, Nottingham, NG7 2UH, UK
SOURCE: European Journal of Cancer (***2002***), 38(4), 505-510
CODEN: EJCAEL; ISSN: 0959-8049
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Matrilysin, a member of matrix ***metalloproteinase*** family, is

believed to play a significant role in the growth and proliferation of colon cancer cells. Overexpression of the matrilysin gene has been shown to correlate with Dukes' stage and increased metastatic potential in colorectal cancer. The aim of this study was to evaluate the effect of preoperative high-dose radiotherapy (25 Gy in five fractions over 5 days) on matrilysin (MMP-7) gene expression, in patients with resectable rectal cancer, by a quant. reverse transcriptase-polymerase chain reaction (RT-PCR). Biopsy samples of tumor (n=30) and distant normal mucosa (n=12) from 15 patients were obtained pre- and post-radiotherapy. Messenger (m)RNA was extracted from all of the tissue samples and reverse transcribed to double-stranded cDNA. Quant. RT-PCR was performed to study the effect of preoperative radiotherapy on matrilysin gene expression in both the tumor and normal mucosal specimens. Matrilysin mRNA values were expressed relative to glyceraldehyde-3-phosphate dehydrogenase (GAPDH) for each sample. In 14 out of 15 cases, matrilysin mRNA was detected in the cancerous tissue. Although all six normal mucosal specimens expressed matrilysin mRNA, the levels were approx. 10-fold lower compared with those seen in the paired tumor samples. Preoperative radiotherapy led to a significant 6- to 7-fold increase (P=0.001) in the expression of matrilysin mRNA in rectal cancer tissue. In contrast, there was no significant change in the matrilysin mRNA expression of normal mucosal specimens post-radiotherapy. Preoperative high-dose radiotherapy upregulates matrilysin gene expression in rectal cancer. Matrilysin ***inhibition*** may be a useful preventive or therapeutic adjunct to radiotherapy in rectal cancer.

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Adachi, Y		45	252	Gut	HCAPLUS
Anon	1997	336	980	N Engl J Med	
Babu, J	1993	165	207	J Immunol Methods	HCAPLUS
Becker-Andre, M	1989	17	9437	Nucliec Acids Res	HCAPLUS
Boag, A	1994	144	585	Am J Path	HCAPLUS
Cedermark, B	1995	75	2269	Cancer	MEDLINE
Chamber, A	1997	89	1260	J Natl Cancer Inst	
Clements, J	1997	74	85	J Neuroimmunol	HCAPLUS
Crabbe, T	1994	345	14	FEBS Lett	HCAPLUS
Davies, B	1993	53	5365	Cancer Res	HCAPLUS
Declerck, Y	1992	52	701	Cancer Res	HCAPLUS
Gaire, M	1994	269	2032	J Biol Chem	HCAPLUS
Gilliland, G	1990	87	2725	Proc Natl Acad Sci U	HCAPLUS
Gridley, D	1998	22	20	Canc Detect Prev	HCAPLUS
Ingber, D	1990	87	3579	Proc Natl Acad Sci U	HCAPLUS
Ishikawa, T	1996	107	5	Cancer Lett	HCAPLUS
Johnson, M	1994	160	194	J Cell Physiol	HCAPLUS
Khokha, R	1992	10	365	Clin Exp Metastasis	HCAPLUS
Kumar, A	2000	84	960	Br J Cancer	
Kumar, A	1999	44	91	Gut	
Marsh, P	1994	37	1205	Dis Colon Rectum	MEDLINE
Mauviel, A	1993	53	288	J Cell Biochem	HCAPLUS
McDonnell, S	1991	4	527	Mol Carcinog	HCAPLUS
McDonnell, S	1990	10	4284	Mol Cell Biol	HCAPLUS
Miyazaki, K	1990	50	7758	Cancer Res	HCAPLUS
Mori, M	1995	75	1516	Cancer	MEDLINE
Muller, D	1993	53	165	Cancer Res	HCAPLUS
Murphy, G	1991	277	277	Biochem J	HCAPLUS
Newell, K	1994	10	199	Mol Carcinog	MEDLINE
Rodgers, W	1993	168	253	Am J Obstet Gynecol	HCAPLUS

Sawaya, R	1994	56	214	Int J Cancer	HCAPLUS
Sheela, S	1986	7	201	Carcinogenesis	HCAPLUS
Simmonds, P	1990	64	864	J Virol	MEDLINE
Tsuchiya, Y	1993	53	1397	Cancer Res	HCAPLUS
Vu, T	1998	93	411	Cell	HCAPLUS
Welch, D	1990	87	7678	Proc Nat Acad Sci (W	HCAPLUS
Wells, G	1996	18	332	Glia	MEDLINE
Wilson, C	1996	28	123	Int J Biochem Cell B	HCAPLUS
Wilson, C	1997	94	1402	Proc Natl Acad Sci U	HCAPLUS
Witty, J	1994	54	4805	Cancer Res	HCAPLUS
Woessner, J	1988	263	16918	J Biol Chem	HCAPLUS
Yashimoto, M	1993	54	614	Int J Cancer	

L18 ANSWER 10 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:560817 HCAPLUS
DOCUMENT NUMBER: 136:65499
TITLE: A novel viper venom ***metalloproteinase***, alborhagin, is an agonist at the platelet collagen receptor GPVI
AUTHOR(S): Andrews, Robert K.; Gardiner, Elizabeth E.; Asazuma, Naoki; Berlanga, Oscar; Tulasne, David; Nieswandt, Bernhard; Smith, A. Ian; Berndt, Michael C.; ***Watson, Stephen P.***
CORPORATE SOURCE: Hazel and Pip Appel Vascular Biology Laboratory, Baker Medical Research Institute, Melbourne, 8008, Australia
SOURCE: Journal of Biological Chemistry (***2001***), 276(30), 28092-28097
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The interaction of platelet membrane glycoprotein VI (GPVI) with collagen can initiate (patho)physiol. thrombus formation. The viper venom C-type lectin family proteins convulxin and alboaggregin-A activate platelets by interacting with GPVI. In this study, the authors isolated from white-lipped tree viper (Trimeresurus albolabris) venom, alborhagin, which is functionally related to convulxin because it activates platelets but is structurally different and related to venom ***metalloproteinases***. Alborhagin-induced platelet aggregation (EC50, <7.5 μg/mL) was ***inhibitable*** by an anti-αIIbβ3 antibody, CRC64, and the Src family kinase ***inhibitor*** PP1, suggesting that alborhagin activates platelets, leading to αIIbβ3-dependent aggregation. Addnl. evidence suggested that, like convulxin, alborhagin activated platelets by a mechanism involving GPVI. First, alborhagin- and convulxin-treated platelets showed a similar tyrosine phosphorylation pattern, including a similar level of phospholipase Cγ2 phosphorylation. Second, alborhagin induced GPVI-dependent responses in GPVI-transfected K562 and Jurkat cells. Third, alborhagin-dependent aggregation of mouse platelets was ***inhibited*** by the anti-GPVI monoclonal antibody JAQ1. Alborhagin had minimal effect on convulxin binding to GPVI-expressing cells, indicating that these venom proteins may recognize distinct binding sites. Characterization of alborhagin as a GPVI agonist that is structurally distinct from convulxin demonstrates the versatility of snake venom toxins and provides a novel probe for GPVI-dependent platelet activation.

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File

Andrews, R	1989	28	8317	Biochemistry	HCAPLUS
Andrews, R	1996	35	12629	Biochemistry	HCAPLUS
Andrews, R	1997	29	91	Int J Biochem Cell B	HCAPLUS
Andrews, R	2000	38	775	Toxicon	HCAPLUS
Asazuma, N	2001	97	3989	Blood	HCAPLUS
Asazuma, N	2000	275	33427	J Biol Chem	HCAPLUS
Berlanga, O	2000	96	2740	Blood	HCAPLUS
Berndt, M	1985	151	637	Eur J Biochem	HCAPLUS
Briddon, S	1999	337	203	Biochem J	
De Luca, M	1995	206	570	Biochem Biophys Res	HCAPLUS
De Luca, M	1995	270	26734	J Biol Chem	HCAPLUS
Dormann, D	2001	97	2333	Blood	
Ezumi, Y	1998	188	267	J Exp Med	HCAPLUS
Falati, S	1999	94	1648	Blood	HCAPLUS
Fujimura, Y	1991	30	1957	Biochemistry	HCAPLUS
Hers, I	2000	267	2088	Eur J Biochem	HCAPLUS
Ichinohe, T	1997	272	63	J Biol Chem	HCAPLUS
Jandrot-Perrus, M	1997	272	27035	J Biol Chem	HCAPLUS
Jeon, O	1999	263	526	Eur J Biochem	HCAPLUS
Khaspekova, S	1993	85	332	Br J Haematol	HCAPLUS
Kini, R	1992	30	265	Toxicon	HCAPLUS
Kini, R	1996	34	1287	Toxicon	HCAPLUS
Kowalska, M	1998	79	609	Thromb Haemostasis	HCAPLUS
Kroll, M	1993	268	3520	J Biol Chem	HCAPLUS
Kulkarni, S	2000	105	783	J Clin Invest	HCAPLUS
Leduc, M	1998	333	389	Biochem J	HCAPLUS
Navdaev, A	2001	276	20882	J Biol Chem	HCAPLUS
Nieswandt, B	2000	275	23998	J Biol Chem	HCAPLUS
Nieswandt, B	2001	193	459	J Exp Med	HCAPLUS
Paine, M	1992	267	22869	J Biol Chem	HCAPLUS
Pasquet, J	1999	342	171	Biochem J	HCAPLUS
Peng, M	1992	67	702	Thromb Haemostasis	HCAPLUS
Polgar, J	1997	272	13576	J Biol Chem	HCAPLUS
Savage, B	1996	84	289	Cell	HCAPLUS
Scholey, J	1980	287	233	Nature	HCAPLUS
Schulte, V	2001	276	364	J Biol Chem	HCAPLUS
Takeya, H	1990	265	16068	J Biol Chem	HCAPLUS
Ward, C	1996	35	4929	Biochemistry	HCAPLUS
Ward, C	1996	34	1203	Toxicon	HCAPLUS
Watson, S	1999	82	365	Thromb Haemostasis	HCAPLUS
Weiss, H	1995	74	117	Thromb Haemostasis	HCAPLUS

L18 ANSWER 11 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:527262 HCAPLUS
DOCUMENT NUMBER: 136:67891
TITLE: Spectrum of matrix ***metalloproteinase*** expression in primary and metastatic colon cancer: Relationship to the tissue ***inhibitors*** of ***metalloproteinases*** and membrane type-1-matrix ***metalloproteinase***
AUTHOR(S): Collins, H. M.; Morris, T. M.; ***Watson, S. A.***
CORPORATE SOURCE: The Academic Unit of Cancer Studies, Division of Gl Surgery, University Hospital, Nottingham, NG7 2UH, UK
SOURCE: British Journal of Cancer (***2001***), 84(12), 1664-1670
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Harcourt Publishers Ltd.
DOCUMENT TYPE: Journal

LANGUAGE: English

AB The matrix ***metalloproteinases***, MMP-2 are MMP-9, are capable of degrading components of the basement membrane, a vital barrier breached during the progression of colorectal cancer. The regulation of MMP-2 activation and subsequent targets is vital to understanding the metastatic process. MMP-2 was not expressed by colorectal cancer cells (C170 and C170HM2) in vitro but by stromal fibroblasts (46BR.1Gl). There was induction of this MMP upon transwell co-cultivation of the colon cancer cells with the fibroblasts but in vivo growth did not lead to a similar increase in the metastatic tumor cells (C170HM2), MMP-2 again being attributed to the stromal cells. MMP-2 mRNA was overexpressed in human colorectal tumors compared to normal colorectal tissue, which correlated with Dukes' stage and immunolocalized to the stromal compartment of the tumor tissue. The active form of the MMP-2 enzyme was also present in the colorectal tumor tissue (7/8) but essentially absent in all normal colon samples examined (1/8). MMP-2 activation was not related to an increase in MT-1-MMP mRNA or a decrease in the specific ***inhibitor*** TIMP-2 in human tissue. There was however an increase in MMP-2/TIMP-2 ratio in tumor compared to normal, MMP-9, a target of active MMP-2, was present in the metastatic cell line but expression was down-regulated in the tumor cells in vivo, gelatin anal. revealed that MMP-9 was almost entirely attributable to the murine host, confirmed by PCR. There was no increase in mRNA for MMP-9 or its specific ***inhibitor*** TIMP-1 in colorectal tumor tissue compared to normal, MMP-9 protein localized to the inflammatory infiltrate. Fibroblast cells may provide malignant epithelial cells with a ready source of enzyme which is crucial to the metastatic process.

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Birkedal-Hanson, H	1993	4	197	Crit Rev Oral Biol M	
Biswas, C	1995	55	434	Cancer Res	HCAPLUS
Brown, P	1990	50	6184	Cancer Res	HCAPLUS
Davies, B	1993	53	5365	Cancer Res	HCAPLUS
Durrant, L	1986	53	37	Br J Cancer	MEDLINE
D'Errico, A	1991	4	239	Mod Pathol	MEDLINE
Ellerbroek, S	1999	59	1635	Cancer Res	HCAPLUS
Fridman, R	1995	55	2548	Cancer Res	HCAPLUS
Harris, E	1990	322	1277	New Engl J Med	
Heppner, K	1996	149	273	Am J Pathol	MEDLINE
Hewitt, R	1991	49	666	Int J Cancer	HCAPLUS
Hyuga, S	1994	54	3611	Cancer Res	HCAPLUS
Lehti, K	1998	334	345	Biochem J	HCAPLUS
Lengyel, E	1995	55	963	Cancer Res	HCAPLUS
Liabakk, N	1996	56	190	Cancer Res	HCAPLUS
Masuda, H	1999	42	393	Dis Colon Rectum	MEDLINE
Masure, S	1993	218	129	Eur J Biochem	HCAPLUS
McDonnell, S	1999	17	341	Clin Exp Metas	MEDLINE
Noel, A	1994	56	331	Int J Cancer	HCAPLUS
Ornstein, D	1999	17	202	Clin Exp Metas	
Page, R	1991	26	230	J Periodont Res	MEDLINE
Parsons, S	1998	78	1495	Br J Cancer	HCAPLUS
Pender, S	1997	158	1582	J Immunol	HCAPLUS
Polette, M	1997	15	157	Clin Exp Metas	MEDLINE
Poulsom, R	1992	141	389	Am J Pathol	MEDLINE
Pyke, C	1993	142	359	Am J Pathol	HCAPLUS
Saito, K	2000	86	24	Int J Cancer	MEDLINE
Sato, H	1994	370	61	Nature	HCAPLUS

Segain, J	1996	56	5506	Cancer Res	HCAPLUS
Shimizu, S	1996	56	3366	Cancer Res	HCAPLUS
Stanton, H	1998	111	2789	J Cell Sci	HCAPLUS
Stetler-Stevenson, W	1993	7	1434	FASEB J	HCAPLUS
Watson, S	1993	29	1740	Eur J Cancer	
Wells, G	1996	18	332	Glia	MEDLINE
Westermarck, J	1999	13	781	FASEB J	HCAPLUS
Zeng, Z	1995	72	575	Br J Cancer	HCAPLUS

L18 ANSWER 12 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:168274 HCAPLUS
DOCUMENT NUMBER: 133:70806
TITLE: Increased type-IV collagenase (MMP-2 and MMP-9) activity following preoperative radiotherapy in rectal cancer
AUTHOR(S): Kumar, A.; Collins, H. M.; Scholefield, J. H.; ***Watson, S. A.***
CORPORATE SOURCE: Academic Unit of Cancer Studies, University Hospital, Nottingham, NG7 2UH, UK
SOURCE: British Journal of Cancer (***2000***), 82(4), 960-965
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Churchill Livingstone
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The aim of this study was to investigate the effect of preoperative high-dose radiotherapy (25 Gy in 5 fractions over 5 days) on the type-IV collagenase protein profile, in patients with resectable rectal cancer, by gelatin zymog. Biopsy samples of tumor and distant normal mucosa from 12 patients with resectable rectal cancer were obtained pre- and post-radiotherapy. Expression of type-IV collagenases (both pro- and active forms) was studied using gelatin zymog. Enzyme levels were normalized for total protein content of each sample. Rectal cancer specimens expressed both pro (72 kDa) and active (62 kDa) forms of MMP-2 but only the pro form of MMP-9 (92 kDa). Normal mucosa showed expression of the pro forms of MMP-2 and MMP-9 while no active form of either enzyme was detected in any of the samples. A significant three- to fourfold increase ($P < 0.01$) of active matrix ***metalloproteinases*** (MMP)-2 (62 kDa) was seen in malignant rectal mucosa after radiotherapy. The effect of radiotherapy also led to a twofold increase ($P = 0.047$) of pro MMP-2 (72 kDa) and a two- to threefold increase ($P = 0.03$) of the precursor form of MMP-9 (92 kDa). In contrast, in normal mucosa expression of the precursor form of MMP-9 (92 kDa) did not change after radiation, and no significant effect on the levels of pro MMP-2 (72 kDa) was observed Preoperative high-dose radiotherapy leads to an increase in activity of type-IV collagenases in patients with resectable rectal cancer. Type-IV collagenase ***inhibition*** may be a useful therapeutic adjunct to radiotherapy in rectal cancer.

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Abulafi, A	1994	81	7	Br J Surg	MEDLINE
Adam, I	1994	344	707	Lancet	MEDLINE
Albini, A	1994	8	1237	AIDS	HCAPLUS
Azzam, H	1993	85	1758	J Natl Cancer Inst	HCAPLUS
Ballin, M	1988	154	832	Biochem Biophys Res	HCAPLUS
Boag, A	1994	144	585	Am J Path	HCAPLUS
Brown, P	1993	11	183	Clin Exp Metastasis	MEDLINE

Cedermark, B	1995	75	2269	Cancer	MEDLINE
Chambers, A	1997	89	1260	J Natl Cancer Inst	HCAPLUS
Chandler, S	1995	201	223	Neurosci Lett	HCAPLUS
Davies, B	1993	67	1126	Br J Cancer	MEDLINE
Davies, B	1993	53	5365	Cancer Res	HCAPLUS
Duffy, M	1998	12	1343	Int J Oncol	HCAPLUS
Heussen, C	1980	102	196	Anal Biochem	HCAPLUS
Jaziorka, M	1994	9	141	Int J Colorectal Dis	
Johnson, M	1994	160	194	J Cell Phys	HCAPLUS
Kinoshita, T	1996	56	2535	Cancer Res	HCAPLUS
Kleiner, D	1994	218	325	Anal Biochem	HCAPLUS
Liabakk, N	1996	56	190	Cancer Res	HCAPLUS
Marsh, P	1994	37	1205	Dis Colon Rectum	MEDLINE
Meyers, M	1989	39	21	CA Cancer J Clin	
Moll, U	1990	50	6162	Cancer Res	HCAPLUS
Moriya, Y	1989	32	307	Dis Colon Rectum	MEDLINE
Muller, D	1993	53	165	Cancer Res	HCAPLUS
Murphy, G	1992	7	120	Am J Resp Cell Mol B	HCAPLUS
Nakajima, M	1990	82	1890	J Natl Cancer Inst	HCAPLUS
Parsons, S	1998	78	1495	Br J Cancer	HCAPLUS
Poulsom, R	1992	141	389	Am J Pathol	MEDLINE
Pyke, C	1993	142	359	Am J Pathol	HCAPLUS
Quirke, P	1986	ii	996	Lancet	
Sawaya, R	1994	56	214	Int J Cancer	HCAPLUS
Seir, C	1996	74	413	Br J Cancer	
Sheela, S	1986	7	201	Carcinogenesis	HCAPLUS
Stetler-Stevenson, W	1993	7	1434	FASEB J	HCAPLUS
Strongin, A	1995	270	5331	J Biol Chem	HCAPLUS
Swedish Rectal Cancer T	1997	336	980	N Engl J Med	
Takahashi, K	1994	93	2357	J Clin Invest	MEDLINE
Tomita, T	1996	39	1255	Dis Colon Rectum	MEDLINE
Turpeenniemi-Hujanen, T	1985	75	99	J Natl Cancer Inst	HCAPLUS
Urbanski, S	1993	2	81	Diag Mol Pathol	MEDLINE
Vu, T	1998	93	411	Cell	HCAPLUS
Yamagata, S	1988	151	158	Biochem Biophys Res	HCAPLUS
Yamagata, S	1991	59	51	Cancer Lett	MEDLINE
Zeng, Z	1995	72	575	Br J Cancer	HCAPLUS
Zeng, Z	1996	14	3133	J Clin Oncol	MEDLINE
Zucker, S	1993	53	140	Cancer Res	MEDLINE

L18 ANSWER 13 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:629238 HCAPLUS
DOCUMENT NUMBER: 132:131883
TITLE: Inhibition of tumor growth by marimastat in a human xenograft model of gastric cancer: relationship with levels of circulating CEA
AUTHOR(S): ***Watson, S. A.***; Morris, T. M.; Collins, H. M.; Bawden, L. J.; Hawkins, K.; Bone, E. A.
CORPORATE SOURCE: Cancer Studies Unit, Department of Surgery, Queen's Medical Centre, Nottingham, UK
SOURCE: British Journal of Cancer (***1999***), 81(1), 19-23
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Churchill Livingstone
DOCUMENT TYPE: Journal
LANGUAGE: English
AB ***Inhibition*** of matrix ***metalloproteinases*** (MMPs) is an attractive approach to adjuvant therapy in the treatment of cancer. Marimastat is the first orally administered, synthetic MMP

inhibitor to be evaluated, in this capacity, in the clinic. Measurement of the rate of change of circulating tumor antigens was used for evaluating biol. activity and defining optimum dosage in the early clin. trials of marimastat. Although tumor antigen levels have been used in the clin. management of cancer for many years, they have not been validated as markers of disease progression. In order to investigate the relationship between the effects of marimastat on tumor growth and circulating tumor antigen levels, mice bearing the human gastric tumor, MGLVA1, were treated with marimastat. The MMP ***inhibitor*** exerted a significant therapeutic effect, reducing tumor growth rate by 48% (P = 0.0005), and increasing median survival from 19 to 30 days (P = 0.0001). In addition, carcinoembryonic antigen (CEA) levels were measured in serum samples from animals sacrificed at regular intervals, and correlated with excised tumor weight It was shown that the natural log of the CEA concentration was linearly related to the natural log of the tumor weight and that treatment was not a significant factor in this relationship (P = 0.7). In conclusion, circulating CEA levels were not directly affected by marimastat, but did reflect tumor size. These results support the use of cancer antigens as markers of biol. activity in early phase trials of non-cytotoxic anticancer agents.

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Allen-Mersh, T	1987	28	1625	Gut	MEDLINE
Anderson, I	1996	56	715	Cancer Res	HCAPLUS
Anon	1981	282	373	Br Med J	
Chirivi, R	1994	58	460	Int J Cancer	HCAPLUS
Cottam, D	1993	2	861	Int J Oncol	HCAPLUS
Davies, B	1993	53	2087	Cancer Res	HCAPLUS
D'Errico, A	1991	4	239	Modern Pathol	MEDLINE
Eccles, S	1996	56	2815	Cancer Res	HCAPLUS
Giavazzi, R	1998	4	985	Clin Cancer Res	HCAPLUS
Goldenberg, D	1981	101	239	J Cancer Res Clin On	HCAPLUS
Gore, M	1996	348	263	Lancet	MEDLINE
Hida, J	1996	39	74	Dis Colon Rectum	MEDLINE
Hine, K	1984	25	682	Gut	MEDLINE
Hojo, J	1977	91	737	Niigata Igakukai Zas	
Honda, M	1996	39	444	Gut	MEDLINE
Kleiner, D	1993	5	891	Curr Opin Cell Biol	HCAPLUS
Liotta, L	1990	1	99	Sem Cancer Biol	MEDLINE
Matrisian, L	1992	14	455	Bioessays	HCAPLUS
McDonnell, S	1991	4	527	Molecular Carcinogen	HCAPLUS
Millar, A	1996	7	123	Ann Oncol	
Millar, A	1996	348	263	Lancet	
Nemunaitis, J	1998	4	1101	Clin Cancer Res	HCAPLUS
Pimm, M	1992	118	367	J Cancer Res and Cli	HCAPLUS
Primrose, J	1999	79	509	Br J Cancer	HCAPLUS
Sledge, G	1995	87	1546	J Natl Cancer Inst	HCAPLUS
Stetler-Stevenson, W	1996	7	147	Semin Cancer Biol	HCAPLUS
Taraboletti, G	1995	87	293	J Natl Cancer Inst	HCAPLUS
Wang, X	1994	54	4726	Cancer Res	HCAPLUS
Ward, U	1993	67	1132	Br J Cancer	MEDLINE
Watson, S	1995	55	3629	Cancer Res	HCAPLUS
Watson, S	1990	45	90	Int J Cancer	HCAPLUS
Watson, S	1991	83	866	J Natl Cancer Inst	MEDLINE

L18 ANSWER 14 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1998:426328 HCAPLUS
DOCUMENT NUMBER: 129:197420
TITLE: Matrix ***metalloproteinase inhibitors*** : a review
AUTHOR(S): ***Watson, Susan A.***; Tierney, Gill
CORPORATE SOURCE: Cancer Studies Unit, Department of Surgery, Queens Medical Centre, University of Nottingham, Nottingham, UK
SOURCE: BioDrugs (***1998***), 9(4), 325-335
CODEN: BIDRF4; ISSN: 1173-8804
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 44 refs. The matrix ***metalloproteinases*** (MMPs) are a family of closely related, zinc-dependent proteolytic enzymes. Collectively, they are capable of degrading all the components of the extracellular matrix and as such are involved in a number of physiol. and pathol. processes. The extracellular matrix is the principal barrier to tumor growth and spread, and there is evidence that MMPs play a role in the processes of tumor growth and metastasis. Therefore, ***inhibitors*** of MMPs may be of value in the treatment of malignant disease. There exist naturally occurring ***inhibitors*** of these enzymes known as "tissue ***inhibitors*** of MMPs", or TIMPs. Although there have been considerable preclin. studies on these ***inhibitors***, they are as yet unavailable for use as therapeutic drugs. Research in this field has focused largely on the development of low mol. weight (<500D) synthetic ***inhibitors*** of MMPs. In this review we focus on the various subgroups of MMP ***inhibitors*** now available, their preclin. evaluation and the limited information available from preliminary clin. trials. We comment on the suitability of the preclin. models used and the difficulty in designing clin. trials of these drugs. We focus on future developments which may involve the use of these drugs in combination with existing chemotherapeutic regimens to achieve a synergistic effect.

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Anderson, I	1996	56	715	Cancer Res	HCAPLUS
Beattie, G	1994			8th NCI-EORTC Sympos	
Bode, W	1994	13	1263	EMBO J	HCAPLUS
Brown, P	1995	6	967	Ann Oncol	MEDLINE
Chander, S	1995	84	404	J Pharm Sci	HCAPLUS
Chirivi, R	1994	58	460	Int J Cancer	HCAPLUS
Davies, B	1993	53	2087	Cancer Res	HCAPLUS
de Takats, P	1996	73	51	Br J Cancer	
Declerck, Y	1991	51	2151	Cancer Res	HCAPLUS
Declerck, Y	1992	52	701	Cancer Res	HCAPLUS
Eccles, S	1996	56	2815	Cancer Res	HCAPLUS
Galardy, R	1994	54	4715	Cancer Res	HCAPLUS
Golub, L	1991	2	297	Crit Rev Oral Biol M	MEDLINE
Jarvinen, M	1987	82	5	Acta Histochem	HCAPLUS
Johnson, W	1987	2	1	Enzyme Inhibition	HCAPLUS
Karakiulakis, G	1990	1035	218	Biochim Biophys Acta	HCAPLUS
Khokha, R	1992	10	365	Clin Exp Metastasis	HCAPLUS
Khokha, R	1994	86	299	J Natl Cancer Inst	HCAPLUS
Kolber, D	1995	87	304	J Natl Cancer Inst	HCAPLUS
Koop, S	1994	54	4791	Cancer Res	HCAPLUS
Lee, W	1991	26	470	J Periodont Res	

Liu, L	1995	62	345	Int J Cancer	HCAPLUS
Macaulay, V	1995	71	11	Br J Cancer	
Maione, T	1990	237	77	Science	
Mignatti, P	1996	47	487	Cell	
Montgomery, A	1994	54	5467	Cancer Res	HCAPLUS
Naito, K	1994	58	730	Int J Cancer	HCAPLUS
Nicoletti, M	1996	32A	6	Eur J Cancer	
Reich, R	1988	48	3307	Cancer Res	HCAPLUS
Richards, C	1993	150	5596	J Immunol	HCAPLUS
Schultz, R	1988	48	5539	Cancer Res	HCAPLUS
Sharpe, R	1990	82	848	J Natl Cancer Inst	HCAPLUS
Sledge, G	1995	87	293	J Natl Cancer Inst	
Stetler-Stevenson, W	1989	264	17374	J Biol Chem	HCAPLUS
Tamargo, R	1991	51	672	Cancer Res	HCAPLUS
Taraboletti, G	1995	87	293	J Natl Cancer Inst	HCAPLUS
Vincenti, M	1994	37	1115	Arthritis Rheum	MEDLINE
Wang, X	1994	54	4726	Cancer Res	HCAPLUS
Watanabe, M	1996	77	1676	Cancer Suppl	HCAPLUS
Watson, S	1996	74	1354	Br J Cancer	HCAPLUS
Watson, S	1996	73	29	Br J Cancer	
Watson, S	1995	55	3629	Cancer Res	HCAPLUS
Zubair, A	1996	73	42	Br J Cancer	
Zucker, M	1991	198	693	Proc Soc Exp Biol Me	HCAPLUS

L18 ANSWER 15 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:707101 HCAPLUS
DOCUMENT NUMBER: 126:604
TITLE: Therapeutic effect of the matrix ***metalloproteinase inhibitor***, batimastat, in a human colorectal cancer ascites model
AUTHOR(S): ***Watson, S. A.***; Morris, T. M.; Parsons, S. L.; Steele, R. J. C.; Brown, P. D.
CORPORATE SOURCE: Cancer Studies Unit, Department Surgery, Queen's Medical Centre, Nottingham, NG7 2UH, UK
SOURCE: British Journal of Cancer (***1996***), 74(9), 1354-1358
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Stockton
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The matrix ***metalloproteinase inhibitor*** batimastat was administered to a human colorectal cancer ascites model, which was initiated by injection of C170HM2 cells into the peritoneal cavity of SCID mice and resulted in solid tumor deposits and ascites formation. The cell line expressed both the 72 and 92 kDa forms of gelatinase by zymog. Batimastat administered from day 0 (40 mg kg-1) reduced the volume of ascites to 21% of control in mice treated from day 0 but not day 10. Formation of solid peritoneal deposits was significantly reduced to 775 of vehicle control when batimastat was administered from day 0 and 695 of control when administered from day 10. Thus, batimastat has the ability to reduce the volume of ascites forming in SCID mice injected i.p. with the human colorectal cell line, C170HM2, when administered from day 0 but not from day 10. Solid peritoneal tumor deposits were significantly reduced in both treatment groups, highlighting the therapeutic potential of batimastat in this clin. condition.

L18 ANSWER 16 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1995:755214 HCAPLUS
DOCUMENT NUMBER: 123:160320

TITLE: ***Inhibition*** of organ invasion by the matrix ***metalloproteinase inhibitor*** batimastat (BB-94) in two human colon carcinoma metastasis models
AUTHOR(S): ***Watson, Susan A.***; Morris, Teresa M.; Robinson, Graham; Crimmin, Michael J.; Brown, Peter D.; Hardcastle, Jack D.
CORPORATE SOURCE: Cancer Studies Unit., Univ. of Hospital, Nottingham, NG7 2RD, UK
SOURCE: Cancer Research (***1995***), 55(16), 3629-33
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of the matrix ***metalloproteinase inhibitor*** batimastat was evaluated in two human colorectal cancer metastasis models involving: (a) the liver-invasive tumor C170HM2 and (b) the lung-invasive tumor AP5LV, both of which have been shown to express the Mr 72,000 type IV collagenase. Batimastat at concns. between 0.01 and 3.0 μg/ml had no direct cytotoxic effects on the in vitro growth of the cell lines. In the liver-invasive tumor model, batimastat administered i.p. from day 10 to termination of the therapy (day 39) at 40 mg/kg reduced both the mean number of liver tumors (35% of vehicle-treated control) and the cross-sectional area of the tumors (43% of vehicle-treated control). In the lung-invasive tumor model, batimastat administered daily (40 mg/kg i.p.) significantly reduced tumor weight within the lung (72% of vehicle-treated control) but did not significantly affect nodule number In the latter model, in which the take rate was unaffected, tumor cells were introduced into the lateral tail vein, and lung localization may have been a phys. phenomenon not involving invasion. In the former model, tumor cells were introduced directly into the peritoneal cavity, and from there the cells adhered to and invaded the liver capsule. Because the take rate is significantly reduced, it may be that the matrix ***metalloproteinases*** are involved in this process. Batimastat may be a therapeutic modality for the treatment of colorectal cancer metastasis.

L18 ANSWER 17 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1991:2486 HCAPLUS
DOCUMENT NUMBER: 114:2486
TITLE: Immunoassays for the detection of human collagenase, stromelysin, tissue ***inhibitor*** of ***metalloproteinases*** (TIMP) and enzyme-***inhibitor*** complexes
AUTHOR(S): Cooksley, Susan; Hipkiss, Jayne B.; Tickle, Simon P.; ***Holmes-Ievers, Eileen***; Docherty, Andrew J. P.; Murphy, Gillian; Lawson, Alastair D. G.
CORPORATE SOURCE: Dep. Immunochem., Celltech Ltd., Slough, SL1 4EN, UK
SOURCE: Matrix (Stuttgart) (***1990***), 10(5), 285-91
CODEN: MTRXEH; ISSN: 0934-8832
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Immunoassays were developed for human collagenase, stromelysin, tissue ***inhibitor*** of ***metalloproteinases*** (TIMP) and TIMP complexed with both of the active enzymes. The selection of antibodies of defined specificity enabled the measurement of both the pro and active forms of the ***metalloproteinase***. Free TIMP was quantified by the selection of a monoclonal antibody which did not recognize TIMP when complexed with ***metalloproteinases***. The detection of enzyme-

inhibitor complexes was achieved by capturing the TIMP component of the complex and revealing the metalloenzyme using specific antibodies.

L18 ANSWER 18 OF 44 MEDLINE on STN
ACCESSION NUMBER: 2002357026 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12099644
TITLE: Emerging biological therapies for pancreatic carcinoma.
AUTHOR: Gilliam Andrew D; ***Watson Susan A***
CORPORATE SOURCE: Academic Unit of Cancer Studies, Department of Surgery Univertisy of Nottingham, Nottingham, NG7 2UH, UK.. andrew.gilliam@nottingham.ac.uk
SOURCE: European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology, ***(2002 Jun)*** Vol. 28, No. 4, pp. 370-8. Ref: 105
Journal code: 8504356. ISSN: 0748-7983.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200208
ENTRY DATE: Entered STN: 9 Jul 2002
Last Updated on STN: 17 Aug 2002
Entered Medline: 16 Aug 2002

AB AIMS: The incidence of pancreatic carcinoma remains approximately equal to its mortality, with the vast majority of patients having advanced disease at presentation. This review is an update of the promising novel approaches involving biological therapy that may be used in conjunction with new chemotherapeutic agents in the near future. MEHTODS: A literature review was performed using the National Library of Medicine's Pubmed database, combined with recently published data from the AGA and ASCO conferences. RESULTS: Rapid progress is being made in gene and molecular technology potentially enabling us to ***inhibit*** pancreatic carcinogenesis and to reduce disease progression. Different targets include signal transduction ***inhibitors***, gene therapy, genetic prodrug activation therapy, antisense therapy, immunotherapy, matrix ***metalloproteinase*** and cyclo-oxygenase-2 ***inhibition*** and hormonal manipulation. CONCLUSION: A variety of biological agents are currently undergoing clinical trials, targeting different areas of the pancreas'neoplastic process. .

L18 ANSWER 19 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1998143455 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9484924
TITLE: Phase I/II trial of batimastat, a matrix ***metalloproteinase inhibitor***, in patients with malignant ascites.
AUTHOR: Parsons S L; ***Watson S A***; Steele R J
CORPORATE SOURCE: Department of Surgery, University Hospital, Nottingham, UK.
SOURCE: European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology, ***(1997 Dec)*** Vol. 23, No. 6, pp. 526-31.
Journal code: 8504356. ISSN: 0748-7983.
PUB. COUNTRY: ENGLAND: United Kingdom

DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
(CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 12 Mar 1998
Last Updated on STN: 3 Mar 2000
Entered Medline: 5 Mar 1998

AB Matrix ***metalloproteinases*** have been shown to be important in tumour invasion and metastasis, and the use of matrix ***metalloproteinase inhibitors*** in animal models has suggested that these agents may be useful in the control of malignant disease. This article reports the results of an early clinical trial of batimastat, one of the first generation of ***metalloproteinase inhibitors***, in patients with malignant ascites. The drug was well absorbed via the intraperitoneal route and associated with few side-effects. Furthermore, a response to treatment was seen in about half the evaluable patients with advanced malignant disease. The results suggest that further research on the use of matrix ***metalloproteinase inhibitors*** in patients with malignant disease is worthwhile.

L18 ANSWER 20 OF 44 MEDLINE on STN
ACCESSION NUMBER: 97204918 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9052425
TITLE: Matrix ***metalloproteinases***.
AUTHOR: Parsons S L; ***Watson S A***; Brown P D; Collins H M; Steele R J
CORPORATE SOURCE: Department of Surgery, University Hospital, Nottingham, UK.
SOURCE: The British journal of surgery, ***(1997 Feb)*** Vol. 84, No. 2, pp. 160-6. Ref: 99
Journal code: 0372553. ISSN: 0007-1323.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199703
ENTRY DATE: Entered STN: 7 Apr 1997
Last Updated on STN: 3 Mar 2000
Entered Medline: 27 Mar 1997

AB BACKGROUND: The matrix ***metalloproteinases*** (MMPs) have a role in gastrointestinal malignancy. This role is reviewed, with particular reference to the gelatinase subgroup of enzymes. METHODS: All relevant papers derived from the Medline and Enbase databases between 1984 and early 1996 were reviewed. RESULT AND CONCLUSION: There is now strong evidence that MMPs play a major role in tumour invasion and metastasis. The development of MMP ***inhibitors*** may lead to important new treatment for the control of malignant disease.

L18 ANSWER 21 OF 44 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:34085 BIOSIS
DOCUMENT NUMBER: PREV200400032181
TITLE: NOVEL ***INHIBITION*** OF MATRIX

METALLOPROTEINASES, ANGIOGENESIS, AND TUMOUR CELL INVASION BY CAPTOPRIL.

AUTHOR(S): Williams, Robert N. [Reprint Author]; Parsons, Simon [Reprint Author]; Rowlands, Brian [Reprint Author]; ***Watson, Susan*** [Reprint Author]

CORPORATE SOURCE: Nottingham, UK

SOURCE: Digestive Disease Week Abstracts and Itinerary Planner, (***2003***) Vol. 2003, pp. Abstract No. W964. e-file.
Meeting Info.: Digestive Disease 2003. FL, Orlando, USA. May 17-22, 2003. American Association for the Study of Liver Diseases; American Gastroenterological Association; American Society for Gastrointestinal Endoscopy; Society for Surgery of the Alimentary Tract.

DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 7 Jan 2004
Last Updated on STN: 7 Jan 2004

AB Introduction: Angiotensin converting enzyme (ACE) is a zinc dependent metallopeptidase derived from the same family of enzymes as the matrix ***metalloproteinases*** (MMPs). These enzymes share structural homology, and their activity is ***inhibited*** by zinc binding compounds. Degradation of the extra cellular matrix (ECM) by MMPs is essential for tumour invasion and angiogenesis. MMP ***inhibition*** has been shown to reduce the invasive potential of malignant cells and represents a therapeutic target. The ACE ***inhibitor*** Captopril, which has a known clinical safety profile, may exert an ***inhibitory*** effect on MMPs and thus possibly ***inhibit*** tumour cell invasion and angiogenesis.Aim: To investigate the effect of Captopril on the expression/activation of MMPs and its ability to ***inhibit*** angiogenesis and tumour cell invasion through extra cellular matrix.Method: Zymography was used to determine the effect of Captopril on the activity of MMP-2 & -9. Effects on MMP gene expression were analysed using real time reverse transcriptase PCR. The functional effect of MMP ***inhibition*** by Captopril on HT1080 tumour cell invasion was determined by matrigel invasion assay. Effects on angiogenesis were determined using TCS cellworks Angiokit containing human umbilical vein endothelial cells (HUVECs).Results: Captopril ***inhibited*** the activity of secreted MMP-2 and -9 in a dose dependent fashion. 5mM Captopril ***inhibited*** the activity of MMP-9 by 41.3% ($p<0.001$) and pro-MMP-2 by 72.8% ($p=0.014$, whilst active MMP-2 was completely ***inhibited***. Zymographic analysis of media conditioned by cells treated with 5mM Captopril showed that the activity of MMP-9, pro- and active MMP-2 was ***inhibited*** by 34.0% ($p=0.009$), 47.2% ($p=0.004$) and 33.7% ($p=0.025$) respectively. Real time PCR did not show any reduction in MMP gene expression with Captopril treatment. The ***inhibition*** of MMP activity by Captopril resulted in a functional reduction in the invasive capacity of HT1080 cells through matrigel. The number of invading cells was ***inhibited*** by 33.7% ($p=0.000$) with 5mM Captopril. Captopril also ***inhibited*** in vitro HUVEC angiogenesis by 27.7% ($p=0.006$).Conclusion: Captopril directly ***inhibits*** the activity of secreted MMPs but also ***inhibits*** MMP production at a post-transcriptional level. Furthermore, Captopril ***inhibits*** the invasion of MMP producing cells through synthetic ECM. The drug also demonstrates the ability to ***inhibit*** angiogenesis. Further work is currently underway to explore the possible therapeutic effects of Captopril on tumours in vivo..

L18 ANSWER 22 OF 44 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:605314 BIOSIS
DOCUMENT NUMBER: PREV200200605314
TITLE: Depletion of interstitial macrophages reduces interstitial fibrosis in experimental hydronephrosis.
AUTHOR(S): Kipari, Tiina M. J. [Reprint author]; Cailhier, Jean-Francois H. [Reprint author]; ***Watson, Simon J. W.*** [Reprint author]; Clay, Michael F. [Reprint author]; Lang, Richard; Hughes, Jeremy [Reprint author]
CORPORATE SOURCE: MRC Centre for Inflammation Research, University of Edinburgh, Edinburgh, UK
SOURCE: Journal of the American Society of Nephrology, (***September, 2002***) Vol. 13, No. Program and Abstracts Issue, pp. 541A. print.
Meeting Info.: Meeting of the American Society of Nephrology. Philadelphia, PA, USA. October 30-November 04, 2002. American Society of Nephrology.
CODEN: JASNEU. ISSN: 1046-6673.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 27 Nov 2002
Last Updated on STN: 27 Nov 2002

L18 ANSWER 23 OF 44 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:408933 BIOSIS
DOCUMENT NUMBER: PREV200200408933
TITLE: Glycine-extended gastrin can promote an increase in pro and active MMP-2 expression at the protein level in cells.
AUTHOR(S): Dean, Richard Asher [Reprint author]; Evans, Sean [Reprint author]; McWilliams, Dan [Reprint author]; ***Watson, Sue A.*** [Reprint author]
CORPORATE SOURCE: Cancer Studies Unit, Nottingham, UK
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (***March, 2002***) Vol. 43, pp. 535. print.
Meeting Info.: 93rd Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA. April 06-10, 2002.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 31 Jul 2002
Last Updated on STN: 23 Sep 2002

L18 ANSWER 24 OF 44 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:509991 BIOSIS
DOCUMENT NUMBER: PREV200200509991
TITLE: Increase in gene and protein expression of gastrin, CCK2R, MMP-2 and TIMP1 in Barrett's compared to paired normal samples.
AUTHOR(S): Harris, J. C. [Reprint author]; Dean, R. A. [Reprint author]; Clarke, P. A. [Reprint author]; Awan, A. [Reprint author]; Jankowski, J.; ***Watson, S. A.*** [Reprint

author]
CORPORATE SOURCE: Academic Unit of Cancer Studies, QMC, University Hospital, Nottingham, NG7 2UH, UK
SOURCE: British Journal of Cancer, (***June, 2002***) Vol. 86, No. Supplement 1, pp. S48-S49. print.
Meeting Info.: British Cancer Research Meeting 2002. Glasgow, UK. June 30-July 03, 2002.
CODEN: BJCAAI. ISSN: 0007-0920.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Oct 2002
Last Updated on STN: 2 Oct 2002

L18 ANSWER 25 OF 44 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:509891 BIOSIS
DOCUMENT NUMBER: PREV200200509891
TITLE: Captopril ***inhibits*** the matrix ***metalloproteinases***: MMP-2 and MMP-9.
AUTHOR(S): Williams, R. N. [Reprint author]; Dean, R. A. [Reprint author]; Parsons, S. L.; Rowlands, B. J.; ***Watson, S. A.*** [Reprint author]
CORPORATE SOURCE: Academic Unit of Cancer Studies, QMC, University Hospital, Nottingham, NG7 2UH, UK
SOURCE: British Journal of Cancer, (***June, 2002***) Vol. 86, No. Supplement 1, pp. S17. print.
Meeting Info.: British Cancer Research Meeting 2002. Glasgow, UK. June 30-July 03, 2002.
CODEN: BJCAAI. ISSN: 0007-0920.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Oct 2002
Last Updated on STN: 2 Oct 2002

L18 ANSWER 26 OF 44 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:235183 BIOSIS
DOCUMENT NUMBER: PREV200100235183
TITLE: Co-culture of human squamous oesophageal and fibroblast cell lines in activation of proMMP-2 resulting in a down regulation of integrin alphaVbeta3 expression and MMP-2, MT1-MMP expression.
AUTHOR(S): Asher-Dean, R. [Reprint author]; Speake, W. J. [Reprint author]; Collins, H. M. [Reprint author]; Jankowski, J.; ***Watson, S. A.*** [Reprint author]
CORPORATE SOURCE: Cancer Studies Unit, Dept of Surgery, QMC, Nottingham, NG7 2UH, UK
SOURCE: Gut, (***March, 2001***) Vol. 48, No. Supplement 1, pp. A68-A69. print.
Meeting Info.: Annual Meeting of the British Society of Gastroenterology. Glasgow, Scotland. March 18, 2001-March 21, 2002. British Society of Gastroenterology.
CODEN: GUTTAK. ISSN: 0017-5749.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English

ENTRY DATE: Entered STN: 16 May 2001
Last Updated on STN: 18 Feb 2002

L18 ANSWER 27 OF 44 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:201148 BIOSIS
DOCUMENT NUMBER: PREV200200201148
TITLE: Enhanced expression of TIMP-1 by Crohn's disease intestinal myofibroblasts: Potential mechanism by which isoforms of TGF-beta may lead to stricture formation.
AUTHOR(S): McKaig, Brian C. [Reprint author]; McWilliams, Dan; ***Watson, Sue A.***; Mahida, Yashwant R.
CORPORATE SOURCE: Div of Gastroenterology, Univ Hosp, Nottingham, UK
SOURCE: Gastroenterology, (***April, 2001***) Vol. 120, No. 5 Supplement 1, pp. A.517. print.
Meeting Info.: 102nd Annual Meeting of the American Gastroenterological Association and Digestive Disease Week. Atlanta, Georgia, USA. May 20-23, 2001. American Gastroenterological Association; American Association for the Study of Liver Diseases; American Society for Gastrointestinal Endoscopy; Society for Surgery of the Alimentary Tract.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 20 Mar 2002
Last Updated on STN: 20 Mar 2002

L18 ANSWER 28 OF 44 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 2000:230052 BIOSIS
DOCUMENT NUMBER: PREV200000230052
TITLE: Expression of matrix ***metalloproteinases*** (MMPs) and tissue ***inhibitors*** of ***metalloproteinases*** (TIMPs) by human intestinal myofibroblasts (IMFs).
AUTHOR(S): Mckaig, B. [Reprint author]; Collins, H.; Hawkey, C. [Reprint author]; ***Watson, S.***; Mahida, Y. [Reprint author]
CORPORATE SOURCE: Division of Gastroenterology, University Hospital, Nottingham, NG7 2UH, UK
SOURCE: Gut, (***April, 2000***) Vol. 46, No. 11, pp. A38. print.
Meeting Info.: 2000 Annual Meeting of the British Society of Gastroenterology. Birmingham, UK. March 21-23, 2000. British Society of Gastroenterology.
CODEN: GUTTAK. ISSN: 0017-5749.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 7 Jun 2000
Last Updated on STN: 5 Jan 2002

L18 ANSWER 29 OF 44 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 2000:257116 BIOSIS
DOCUMENT NUMBER: PREV200000257116
TITLE: Expression of matrix ***metalloproteinases*** (MMPs)

and tissue ***inhibitors*** of ***metalloproteinases*** (TIMPs) by human intestinal myofibroblasts.
AUTHOR(S): McKaig, Brian C. [Reprint author]; Collins, Hilary; Hawkey, Christopher J.; ***Watson, Sue***; Mahida, Yashwant R.
CORPORATE SOURCE: Div of Gastroenterology, Univ of Nottingham, Nottingham, UK
SOURCE: Gastroenterology, (***April, 2000***) Vol. 118, No. 4 Suppl. 2 Part 1, pp. AGA A551. print.
Meeting Info.: 101st Annual Meeting of the American Gastroenterological Association and the Digestive Disease Week. San Diego, California, USA. May 21-24, 2000. American Gastroenterological Association.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 21 Jun 2000
Last Updated on STN: 5 Jan 2002

L18 ANSWER 30 OF 44 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 1998:286830 BIOSIS
DOCUMENT NUMBER: PREV199800286830
TITLE: A phase II study of the oral matrix ***metalloproteinase inhibitor***, marimastat, in patients with inoperable gastric cancer.
AUTHOR(S): Tierney, G.; Parsons, S. L.; Griffin, N. R.; ***Watson, S. A.***; Steele, R. J. C.
CORPORATE SOURCE: Dep. Surg., Univ. Hosp., Nottingham, UK
SOURCE: Gastroenterology, (***April 15, 1998***) Vol. 114, No. 4 PART 2, pp. A688. print.
Meeting Info.: Digestive Disease Week and the 99th Annual Meeting of the American Gastroenterological Association. New Orleans, Louisiana, USA. May 16-22, 1998. American Gastroenterological Association.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 8 Jul 1998
Last Updated on STN: 13 Aug 1998

L18 ANSWER 31 OF 44 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 1997:279462 BIOSIS
DOCUMENT NUMBER: PREV199799578665
TITLE: A phase i/ii study of oral matrix ***metalloproteinase inhibitor***, marimastat, in patients with inoperable gastric cancer.
AUTHOR(S): Parsons, S. L.; ***Watson, S. A.***; Griffin, N. R.; Tierney, G. M.; Steele, R. J. C.
CORPORATE SOURCE: Dep. Surgery Pathol., Univ. Hosp., Nottingham, UK
SOURCE: Gastroenterology, (***1997***) Vol. 112, No. 4 SUPPL., pp. A636.
Meeting Info.: Digestive Disease Week and the 97th Annual Meeting of the American Gastroenterological Association. Washington, D.C., USA. May 11-14, 1997.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)

Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Jul 1997
Last Updated on STN: 5 Aug 1997

L18 ANSWER 32 OF 44 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 1996:299159 BIOSIS
DOCUMENT NUMBER: PREV199699021515
TITLE: Phase I/II trial of a matrix ***metalloproteinase inhibitor*** in patients with malignant ascites.
AUTHOR(S): Parsons, S. L.; ***Watson, S. A.***; Amar, S. S.; Steele, R. J. C.
CORPORATE SOURCE: Dep. Surg., Univ. Hosp., Nottingham NG7 2UH, UK
SOURCE: Gastroenterology, (***1996***) Vol. 110, No. 4 SUPPL., pp. A575.
Meeting Info.: 96th Annual Meeting of the American Gastroenterological Association and the Digestive Disease Week. San Francisco, California, USA. May 19-22, 1996.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Jul 1996
Last Updated on STN: 2 Jul 1996

L18 ANSWER 33 OF 44 DRUGU COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-27672 DRUGU B P
TITLE: ***Inhibition*** of matrix ***metalloproteinase*** 2 and 9 by the angiotensin converting enzyme ***inhibitor*** captopril.
AUTHOR: Williams R N; Dean R A; Parsons S L; Rowlands B J; ***Watson S A***
CORPORATE SOURCE: Univ.Nottingham
LOCATION: Nottingham, U.K.
SOURCE: Br.J.Surg. (90, No. 5, 617, 2003)
CODEN: BJSUAM ISSN: 0007-1323
AVAIL. OF DOC.: Academic Unit of Cancer Studies, Department of Surgery, University of Nottingham, Nottingham, U.K.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 2003-27672 DRUGU B P
AB Matrix ***metalloproteinase*** (MMP) gene expression in human fibrosarcoma cells in-vitro was not affected by captopril (0.25-5 mM). The activity of secreted MMPs was reduced dose-dependently with the maximal effect seen at 5 mM. Pro-MMP-2 and MMP-9 activity were reduced by 72.8% and 41.3%, respectively and active MMP-2 was abolished. Cellular production of MMPs was reduced by 5 mM captopril with Pro-MMP-2 and MMP-9 reduced by 47.2% and 33.7% respectively with a 40.0% reduction in active MMP-2. HT-1080 tumors were implanted in nude mice to determine the effect of Captopril (200 mg/kg) on tumor growth. The in-vivo growth of HT1080 was ***inhibited*** by 53.5%. Captopril ***inhibits*** MMP production and activation which translates into a therapeutic action on in vivo tumor growth. (conference abstract: 3rd Meeting of the Society of Academic and Research Surgery, Leeds, U.K., January, 2003). (No EX).
ABEX (KL)

L18 ANSWER 34 OF 44 DRUGU COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-20928 DRUGU P
TITLE: Novel ***inhibition*** of matrix ***metalloproteinases***, angiogenesis, and tumour cell invasion by captopril.
AUTHOR: Williams R N; Parsons S; Rowlands B; ***Watson S***
LOCATION: USA
SOURCE: ; Digestive Dis. Week (106925, 2003)
CODEN: ; 9999
AVAIL. OF DOC.: No Reprint Address.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 2004-20928 DRUGU P
AB In-vitro, captopril ***inhibited*** matrix ***metalloproteinases*** (MMP), angiogenesis and tumor cell invasion through extracellular matrix. (conference abstract: Digestive Disease Week 2003, Orlando, Florida, USA, May 18-21, 2003).
ABEX Methods Zymography was used to determine effect of captopril on activity of MMP-2 and MMP-9. Effects on MMP gene expression were analyzed using real-time reverse transcriptase PCR. Functional effect of MMP ***inhibition*** by captopril on HCT1080 cell invasion was determined by matrigel invasion assay. Effects on angiogenesis were determined using TCS cellworks Angiokit containing human umbilical vein endothelial cells (HUVEC). Results Captopril ***inhibited*** activity of secreted MMP-2 and MMP-9 in a dose-dependent manner. In particular, 5 mM captopril ***inhibited*** activity of MMP-9 by 41.3% and pro-MMP-2 by 72.8%, while active MMP-2 was completely ***inhibited***. Zymographic analysis of media conditioned by cells exposed to 5 mM captopril demonstrated that activity of MMP-9, pro-MMP-2 and active MMP-2 was ***inhibited*** by 34.0%, 47.2% and 33.7%, respectively. Real-time PCR did not demonstrate any down-regulation of MMP gene expression with captopril. ***Inhibition*** of MMP activity by captopril caused a functional reduction in invasive capacity of HT1080 cells through matrigel. Number of invading cells was decreased by 33.7% with 5 mM captopril. Captopril also ***inhibited*** HUVEC angiogenesis by 27.7%. (E42/JM)

L18 ANSWER 35 OF 44 DRUGU COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-32707 DRUGU P B
TITLE: Captopril ***inhibits*** the matrix ***metalloproteinases***: MMP-2 and MMP-9.
AUTHOR: Williams R N; Dean R A; Parsons S L; Rowlands B J; ***Watson S A***
CORPORATE SOURCE: Univ.Nottingham
LOCATION: Nottingham, U.K.
SOURCE: Br.J.Cancer (86, Suppl. 1, S17, 2002)
CODEN: BJCAAI ISSN: 0007-0920
AVAIL. OF DOC.: Academic Unit of Cancer Studies, University Hospital, Nottingham, NG7 2UH, England.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 2002-32707 DRUGU P B
AB The effect of captopril on the matrix ***metalloproteinases*** MMP-2 and MMP-9 was investigated in HT1080 cells in-vitro. The results suggested that captopril ***inhibited*** MMP-2 and MMP-9, by binding

to their active site. The ***inhibition*** of MMP activity produced by captopril in cell culture was greater than its ***inhibitory*** effect on cell proliferation. This suggests that captopril may ***inhibit*** other cellular pathways and that the reduction in MMP activity was not only a reflection of the reduction in cell population. (conference abstract: British Cancer Research Meeting, Glasgow, U.K., 2002).

ABEX Gelatin zymography was used to investigated captopril ***inhibition*** of MMP-2 and MMP-9. Captopril ***inhibited*** both MMP-2 and -9 dose-dependently when added to zymography developing buffer. MMP-9 was ***inhibited*** to 70.7%, 64.8% and 46.9% of control values by 500 uM, 1 mM and 2.5 mM captopril, respectively. Active MMP-2 was ***inhibited*** to 23.4% and 9.3% by 250 uM and 500 uM captopril, respectively. The addition of 5 mM captopril to cell culture of HT1080 produced ***inhibition*** of MMP-9 activity to 65% of control values and 75% of control values for active MMP-2 activity. Captopril at 5 mM ***inhibited*** the proliferation of HT1080 cells. The population of cells treated with 5 mM captopril was only 84% of the untreated control population. (DAC)

L18 ANSWER 36 OF 44 DRUGU COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 1998-43928 DRUGU P B
TITLE: Therapeutic effect of the matrix ***metalloproteinase*** (MMP) ***inhibitor***, marimastat, in a gastric cancer xenograft model: relationship to MMP messenger RNA levels.
AUTHOR: Tierney G M; Collins H M; Morris T M; Scholefield J H; ***Watson S A***
CORPORATE SOURCE: Univ.Nottingham
LOCATION: Nottingham, U.K.
SOURCE: Br.J.Surg. (85, No. 11, 1562, 1998)
CODEN: BJSUAM ISSN: 0007-1323
AVAIL. OF DOC.: Academic Unit of Cancer Studies, Division of Gastrointestinal Surgery, University of Nottingham, Nottingham, England.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1998-43928 DRUGU P B
AB The effect of marimastat (MM) on the growth and MMP expression of human gastric xenografts, MKN45G and ST-16, was evaluated in mice and any observed effect was related to a change in MMP mRNA level. Results showed that MM caused ST-16 xenografts to become macroscopically undetectable. (conference abstract).
ABEX Methods MKN45G and ST-16 tissue was s.c. implanted into nude mice. MM (50 mg/kg) was administered daily, and animals were sacrificed at day 28. Xenograft tissue was extracted, and mRNA was evaluated using PCR. Results ST-16 tumors were not detected macroscopically after MM treatment.reverse-transcriptase PCR demonstrated mRNAs for MMP-2, MMP-7 and MMP-9, tissue inhibitors of MMPs (TIMPs) 1 and 2, and MT-MMP-1 in all control samples. MKN45G showed a significant reduction in mRNA for MT-MMP-1 after treatment. (KH)

L18 ANSWER 37 OF 44 DRUGU COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 1999-01111 DRUGU P
TITLE: Therapeutic effect of the matrix ***metalloproteinase*** ***inhibitor***, marimastat in a gastric cancer xenograft model: relationship to CEA levels.
AUTHOR: ***Watson S A***; Morris T M; Collins H M; Tierney G; Bawden L J; Hawkins K

CORPORATE SOURCE: Univ.Nottingham; British-Biotech.
LOCATION: Nottingham, U.K.
SOURCE: Br.J.Cancer (78, Suppl. 1, 50, 1998)
CODEN: BJCAAI ISSN: 0007-0920
AVAIL. OF DOC.: Academic Unit of Cancer Studies, Division of GI Surgery, University of Nottingham, Nottingham, England.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1999-01111 DRUGU P
AB The effect of the broad spectrum MMP inhibitor marimastat was studied on the growth of a CEA-secreting human gastric xenograft, MGLVA1, allowing any relationship between therapeutic effect and serum CEA levels to be determined in mice. Marimastat was shown to significantly inhibit tumor size in both male and female mice when compared with the respective vehicle controls.
ABEX For the therapy experiments MGLVA1 tissues was implanted s.c. into both male and female nude mice. Dosing with marimastat (15 mg/ml in osmotic pump is equivalent to approximately 7.2 mg/kg/day) began on day 1 and continued throughout the course of the experiment. Marimastat was shown to significantly inhibit tumor size in both male and female mice when compared with the respective vehicle controls. Marimastat also exerted a significant effect of survival with median survival increasing from 18 days to 30 days. A further experiment was designed to asses the effect of marimastat in circulating CEA levels. Marimastat or vehicle was delivered as above, and the ability of marimastat to significantly inhibit tumor growth was confirmed. Throughout the course of the experiment 4 animals of each sex from both treated and control groups were sacrificed at regular intervals and serum samples were collected for CEA analysis. The log of CEA concentration was linearly related to log of the tumor weight, irrespective of whether the tumor derives from a marimastat or vehicle treated animal. (KJ)

L18 ANSWER 38 OF 44 DRUGU COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 1998-45299 DRUGU T P S
TITLE: A phase II study of the oral matrix ***metalloproteinase inhibitor***, marimastat, in patients with inoperable gastric cancer.
AUTHOR: Tierny G; Parsons S L; Griffin N R; ***Watson S A***; Steele R J C
LOCATION: Nottingham, U.K.
SOURCE: Gastroenterology (114, No. 4, Pt. 2, A688, 1998)
CODEN: GASTAB ISSN: 0016-5085
AVAIL. OF DOC.: Department of Surgery, University Hospital, Nottingham, England.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1998-45299 DRUGU T P S
AB The matrix ***metalloproteinases*** (MMPs) are a family of proteolytic enzymes involved in turnover of the extracellular matrix and have been implicated in the process of tumor growth and metastasis. The aim of this study was to confirm the safety of a 4 wk course of marimastat, to assess the tumors at endoscopy and examine biopsies histologically, to quantify tumor MMPs prior to and after treatment in 25 patients with advanced gastric adenocarcinoma. The side-effects were musculoskeletal, appeared dose-related and resolved after a treatment

break. The study demonstrated good oral bioavailability of marimastat. Side-effects appear dose-related and reversible. These effects may be due to ***inhibition*** of collagenase in peri-articular tissues. A prospective, randomized, placebo-controlled study of this treatment is currently underway. (conference abstract).

ABEX The aim of this study was to confirm the safety of a 4 wk course of marimastat, to assess the tumors at endoscopy and examine biopsies histologically and using zymography, to quantify tumor MMPs prior to and after treatment. 25 Patients with advanced gastric adenocarcinoma underwent pre-dose endoscopy and biopsy of the tumor. They received marimastat at a dose of 50 mg b.i.d. (1st 6 patients) or 25 mg once daily (all subsequent patients). Endoscopy was performed at day 28. Patients with a response to the treatment or static disease in the absence of side-effects were selected to continue. Biopsies were sent for histology and gelatin zymography. Both doses gave adequate plasma drug levels (mean trough level: 260 u/l on 50 mg, b.d., 50 u/l on 25 mg, o.d.). 15 Patients had continued use of the drug, 9 on the basis of response (defined as decreased tumor vascularity, evidence of stroma formation or decreased size). The side-effects were musculoskeletal; arose after 28 days of treatment, appeared dose-related and resolved after a treatment break. There was no difference in the zymography profile after treatment. This study has demonstrated good oral bioavailability of marimastat. Side-effects appear dose-related and reversible. These effects may be due to ***inhibition*** of collagenase in peri-articular tissues. A prospective, randomized, placebo-controlled study of this treatment is currently underway. (LJ)

L18 ANSWER 39 OF 44 DRUGU COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 1997-26528 DRUGU T S
TITLE: A phase I/II study of the oral matric ***metalloproteinase inhibitor***, marimastat, in patients with inoperable gastric cancer.
AUTHOR: Parsons S L; ***Watson S A***; Griffin N R; Tierney G M; Steele R J C
LOCATION: Nottingham, U.K.
SOURCE: Gastroenterology (112, No. 4, Suppl., A636, 1997)
CODEN: GASTAB ISSN: 0016-5085
AVAIL. OF DOC.: Department of Surgery and Pathology, University Hospital, Nottingham, England.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1997-26528 DRUGU T S
AB Matrix ***metalloproteinases*** (MMPs) play an important role in tumor invasion and metastasis. Marimastat (SC-44463) is the 1st p.o. active synthetic MMP ***inhibitor*** and was given to 14 patients with inoperable gastric cancer, in a phase I/phase II study. Musculoskeletal pain and restriction of movement were identified as the principle treatment-related side-effects and led to a reduction in dose. It is concluded that a dose of 25 mg/day appears to be well-tolerated in patients with inoperable gastric cancer. There are early indications that marimastat may slow the rate of progression of gastric cancer. (conference abstract).

ABEX MMPs play an important role in tumor invasion and metastasis. Marimastat is the 1st orally active synthetic MMP ***inhibitor*** and was given to 14 patients for 28 days. An endoscopic examination and biopsy was performed at entry and at 28 days of treatment. Safety and tolerability were assessed and biopsy samples analyzed histologically. Patients who

showed no evidence of progression endoscopically were eligible for continued treatment. 14 Patients completed the 28 day study period (median age 70.4 yr, range 45-85, 9 male). 7 Patients showed no evidence of progression at the 28 day endoscopic examination and continued to take marimastat. 2 Patients showed histological and macroscopic changes in tumor appearance with decreased tumor cellularity and increased stromal tissue for 15 and 4 mth, respectively. Macroscopic changes consistent with stromal formation were observed in the tumors of 3 other patients. Musculoskeletal pain and restriction of movement were identified as the principle treatment-related side-effects and led to a reduction in dose. A dose of 25 mg/day appears to be well-tolerated in patients with inoperable gastric cancer. There are early indications that marimastat may slow the rate of progression of gastric cancer. (LJ)

L18 ANSWER 40 OF 44 DRUGU COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 1998-03614 DRUGU B T
TITLE: Gelatinase profile in advanced gastric cancer before and after treatment with a matrix ***metalloproteinase inhibitor***.
AUTHOR: Tierney G; Collins H M; Parsons S; ***Watson S***; Steele R J C
CORPORATE SOURCE: Univ.Nottingham
LOCATION: Nottingham, U.K.
SOURCE: Gut (41, Suppl. 3, A151, 1997)
CODEN: GUTTAK ISSN: 0017-5749
AVAIL. OF DOC.: Dept. of Surgery, University Hospital, Nottingham, England.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1998-03614 DRUGU B T
AB Marimastat (BB-2516; British-Biotech.) did not affect the enzyme profile of a gastric cancer biopsy obtained from patients who received the drug, a matrix ***metalloproteinases inhibitor***, as part of a phase II trial. The 92 kDa and the 72 kDa gelatinases were expressed in the tumor biopsies both prior to and after treatment with marimastat. Their active forms (82 kDa and 62 kDa) were also identified on the gels. After treatment there was no significant change in the quantity of active or inactive enzyme. These results indicate that marimstat does not convert the malignant-associated gelatinase to the benign form of enzyme. (conference abstract). (No EX.).
ABEX (VH)

L18 ANSWER 41 OF 44 DRUGU COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 1996-30339 DRUGU P
TITLE: Combined therapeutic effect of marimastat and cisplatin on the in vivo growth of a human small cell lung cancer.
AUTHOR: ***Watson S A***; Morris T M; Parsons S; Steele R J C; Drummond A; Brown P
CORPORATE SOURCE: Univ.Nottingham; British-Biotechnol.
LOCATION: Nottingham; Oxford, U.K.
SOURCE: Br.J.Cancer (73, Suppl. 26, 29, 1996)
CODEN: BJCAAI ISSN: 0007-0920
AVAIL. OF DOC.: Cancer Studies Unit, Department of Surgery, University of Nottingham NG7 2UH, England.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

AN 1996-30339 DRUGU P
AB Combined antitumor effects of the matrix ***metalloproteinase*** (MMP) ***inhibitor***, p.o. marimastat (SC-44463, MS), with i.v. cisplatin (CP), were evaluated against human small cell lung tumor xenografts in nude mice. The observed increased therapeutic effectiveness with the combination may have been the result of the 2 agents ***inhibiting*** tumor growth through independent mechanisms. (conference abstract).
ABEX Overproduction of MMPs appears to play an important role in tumor metastasis due to an increased ability to both break down the basement membrane and promote neo-vascularization. Thus ***inhibitors*** of such enzymes may have a therapeutic role. The human small cell lung tumor line, 841, has been shown to express the 92 and 72kDa forms of gelatinase by zymography and be sensitive to the antiproliferative effects of cisplatin. Thus, it was decided to evaluate both the individual and combined effects of MS (50 mg/kg, b.i.d.) and CP (4 mg/kg) on the subcutaneous growth of 841 tumors in MF1 nude mice. At day 20, the cross-sectional area of tumors in the vehicle control group (mean of 265.0 sq.m) were significantly greater than in the MS-treated group (190.3 sq.m), the CP group (101.5 sq.m) and the combination (57.6 sq.m).The combination was significantly smaller than the 2 treatments given individually. The time taken for tumors to reach a size greater than 300 sq.m was evaluated for each treatment group. Vehicle control-treated animals were terminated by day 31 compared to day 38 for MS alone, day 43 for CP and day 70 for animals treated with the combination. (E54/RSV)

L18 ANSWER 42 OF 44 DRUGU COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 1996-38650 DRUGU T P S
TITLE: Phase I/II trial of a matric ***metalloproteinase inhibitor*** in patients with malignant ascites.
AUTHOR: Parsons S L; ***Watson S A***; Amar S S; Steele R J C
CORPORATE SOURCE: Univ.Nottingham
LOCATION: Nottingham, U.K.
SOURCE: Gastroenterology (110, No. 4, Suppl., A575, 1996)
CODEN: GASTAB ISSN: 0016-5085
AVAIL. OF DOC.: Department of Surgery, University Hospital, Nottingham, England, NG7 2UH.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1996-38650 DRUGU T P S
AB In a phase I/II trial, 9 patients (pts) with malignant ascites underwent i.p. administration of a suspension of a synthetic matrix ***metalloproteinase inhibitor*** (Batimastat) after removal of an equal volume of ascites. Rapid systemic drug absorption was achieved with drug levels remaining elevated for 6 wk and were higher than in a corresponding study where the ascites was drained to dryness prior to drug administration. Side-effects consisted of abdominal pain, scrotal edema, pyrexia, nausea and vomiting. A treatment response was seen in most pts. Thus, i.p. Batimastat is well absorbed and the large Vd (ascites not drained) improved absorption. Our results suggest that this agent may be useful in controlling ascites though further studies are required to confirm this. (conference abstract).
ABEX Methods 9 Pts with proven malignant ascites were recruited and underwent i.p. administration of a 500 ml suspension of Batimastat after removal of an equal volume of ascites. Response to treatment was assessed by weight, abdominal girth and drainage. Results Rapid

systemic drug absorption was achieved with drug levels remaining elevated for 6 wk and were higher than in a corresponding study where the ascites was drained to dryness prior to drug administration. Side-effects consisted of abdominal pain of mild-to-moderate intensity (6 pts), pyrexia (2 pts), nausea (3 pts) and vomiting (2 pts). Only abdominal pain (3 pts) and scrotal oedema continued beyond 72 hr. A treatment response was seen in 5/9 patients. (SA)

L18 ANSWER 43 OF 44 DRUGU COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 1996-18382 DRUGU T B S
TITLE: Phase I/II trial of a matrix ***metalloproteinase inhibitor*** in patients with malignant ascites.
AUTHOR: Parsons S L; ***Watson S A***; Amar S S; Steele R J C
CORPORATE SOURCE: Univ.Nottingham
LOCATION: Nottingham, U.K.
SOURCE: Gut (38, Suppl. 1, A18, 1996)
CODEN: GUTTAK ISSN: 0017-5749
AVAIL. OF DOC.: Department of Surgery, University Hospital, Nottingham, England NG7 20H.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1996-18382 DRUGU T B S
AB Intraperitoneal Batimastat successfully controlled ascites in 9 patients with malignant ascites in a phase I/II trial. Side-effects included abdominal pain of mild to moderate intensity, pyrexia, nausea and vomiting. A treatment response was seen in 5/9 patients. Intraperitoneal Batimastat was well absorbed and the large volume of dissolution (ascites not drained) improved absorption. Batimastat may be useful in controlling ascites though further studies are required to confirm this. (conference abstract).
ABEX Nine patients with malignant ascites underwent intraperitoneal administration of a 500 ml suspension of Batimastat after removal of an equal volume of ascites. Response to treatment was assessed by weight, abdominal girth and drainage. Rapid systemic drug absorption was achieved. Drug levels remained elevated for 6 weeks. Only abdominal pain and scrotal edema continued beyond 72 hr. (COS)

L18 ANSWER 44 OF 44 DRUGU COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 1994-23213 DRUGU P
TITLE: The matrix ***metalloproteinase inhibitor*** BB94 ***inhibits*** experimental metastasis and ascites formation of the human colorectal tumour, C170HM2.
AUTHOR: ***Watson S A***; Brown P D; Morris T M; Robinson G; Hardcastle J D
LOCATION: Nottingham, Oxford, United Kingdom
SOURCE: Br.J.Cancer (69, Suppl. 21, 19, 1994)
CODEN: BJCAAI ISSN: 0007-0920
AVAIL. OF DOC.: Department of Surgery, Queen's Medical center, Nottingham, NG7 2RD, England.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1994-23213 DRUGU P
AB Matrix ***metalloproteinases*** are known to play a role in the progression of human colorectal cancer. In the present study, the ***metalloproteinase inhibitor***, BB94, given by the i.p.

route, ***inhibited*** experimental metastasis and ascites formation of a human colorectal tumor cell-line, C170HM2, in nude mice. Agents which ***inhibit*** the activity of invasive enzymes may reduce tumor spread and may therefore be of clinical value. (congress abstract).

ABEX C170HM2 has been selected to invade the liver following i.p. injection into nude mice. The C170HM2 tumors express both interstitial collagenase, at the leading edge of the tumor, and 72kDa gelatinase, during invasion within the liver. BB94 was administered at a dose of 40 mg/kg, i.p., from day 10 to the end of the study (day 39) and was shown to significantly reduce both the number (35% of vehicle-treated controls) and the cross-sectional area (73% of control) of the liver tumors. Histological analysis showed that the zone of proliferative cells was reduced and necrosis within the tumors was more advanced in the BB94-treated group. An ascites variant of C170HM2 has been derived in SCID mice following i.p. administration of cells. BB94 given from day 0, at the same dosage schedule as described, reduced (i) the number of mice developing ascites from 100% to 53%; (ii) the mean ascites volume from 1.78 ml to 0.38 ml; and (iii) peritoneal tumor weight from 2.19 g to 1.70 g. All the in-vivo studies were performed according to the UK coordinating committee for Cancer Research Guidelines. (NPH)